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(54) **2-(4-Hydroxyphenyl)benzothiophene compounds, compositions and methods for alleviating the symptoms of post-menopause syndrome**

2-(4-Hydroxyphenyl)-benzothiophen-Derivate, Zubereitungen und Methoden zur Milderung der Symptome des post-menopausalen Syndroms

Dérivés de 2-(4-hydroxyphényle)benzothiophène, compositions et procédés destinés à réduire les symptômes de la post-ménopause

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EP-A- 0 062 503 **EP-A- 0 516 257**
WO-A-93/10113 **WO-A-95/10513**

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Description

[0001] This invention relates to the fields of pharmaceutical and organic chemistry and provides novel benzothio-
phene compounds which are useful for the treatment of the various medical indications associated with post-meno-
pausal syndrome, and uterine fibroid disease, endometriosis, and aortal smooth muscle cell proliferation. The present
invention also relates to pharmaceutical compositions of the compounds of the present invention, and further relates
to a novel process for preparing the pharmaceutically active compounds of the present invention.

[0002] "Post-menopausal syndrome" is a term used to describe various pathological conditions which frequently
affect women who have entered into or completed the physiological metamorphosis known as menopause. Although
numerous pathologies are contemplated by the use of this term, three major effects of post-menopausal syndrome are
the source of the greatest long-term medical concern: osteoporosis, cardiovascular effects such as hyperlipidemia,
and estrogen-dependent cancer, particularly breast and uterine cancer.

[0003] Osteoporosis describes a group of diseases which arise from diverse etiologies, but which are characterized
by the net loss of bone mass per unit volume. The consequence of this loss of bone mass and resulting bone fracture
is the failure of the skeleton to provide adequate structural support for the body. One of the most common types of
osteoporosis is that associated with menopause. Most women lose from about 20% to about 60% of the bone mass
in the trabecular compartment of the bone within 3 to 6 years after the cessation of mensus. This rapid loss is generally
associated with an increase of bone resorption and formation. However, the resorptive cycle is more dominant and the
result is a net loss of bone mass. Osteoporosis is a common and serious disease among post-menopausal women.

[0004] There are an estimated 25 million women in the United States, alone, who are afflicted with this disease. The
results of osteoporosis are personally harmful and also account for a large economic loss due its chronicity and the
need for extensive and long term support (hospitalization and nursing home care) from the disease sequelae. This is
especially true in more elderly patients. Additionally, although osteoporosis is not generally thought of as a life threat-
ening condition, a 20% to 30% mortality rate is related with hip fractures in elderly women. A large percentage of this
mortality rate can be directly associated with post-menopausal osteoporosis.

[0005] The most vulnerable tissue in the bone to the effects of post-menopausal osteoporosis is the trabecular bone.
This tissue is often referred to as spongy or cancellous bone and is particularly concentrated near the ends of the bone
(near the joints) and in the vertebrae of the spine. The trabecular tissue is characterized by small osteoid structures
which inter-connect with each other, as well as the more solid and dense cortical tissue which makes up the outer
surface and central shaft of the bone. This inter-connected network of trabeculae gives lateral support to the outer
cortical structure and is critical to the biomechanical strength of the overall structure. In post-menopausal osteoporosis,
it is, primarily, the net resorption and loss of the trabeculae which leads to the failure and fracture of bone. In light of
the loss of the trabeculae in post-menopausal women, it is not surprising that the most common fractures are those
associated with bones which are highly dependent on trabecular support, e.g., the vertebrae, the neck of the weight
bearing bones such as the femur and the fore-arm. Indeed, hip fracture, collics fractures, and vertebral crush fractures
are hall-marks of post-menopausal osteoporosis.

[0006] At this time, the only generally accepted method for treatment of post-menopausal osteoporosis is estrogen
replacement therapy. Although therapy is generally successful, patient compliance with the therapy is low primarily
because estrogen treatment frequently produces undesirable side effects.

[0007] Throughout premenopausal time, most women have less incidence of cardiovascular disease than age-
matched men. Following menopause, however, the rate of cardiovascular disease in women slowly increases to match
the rate seen in men. This loss of protection has been linked to the loss of estrogen and, in particular, to the loss of
estrogen's ability to regulate the levels of serum lipids. The nature of estrogen's ability to regulate serum lipids is not
well understood, but evidence to date indicates that estrogen can upregulate the low density lipid (LDL) receptors in
the liver to remove excess cholesterol. Additionally, estrogen appears to have some effect on the biosynthesis of
cholesterol, and other beneficial effects on cardiovascular health.

[0008] It has been reported in the literature that post-menopausal women having estrogen replacement therapy have
a return of serum lipid levels to concentrations to those of the pre-menopausal state. Thus, estrogen would appear to
be a reasonable treatment for this condition. However, the side-effects of estrogen replacement therapy are not ac-
ceptable to many women, thus limiting the use of this therapy. An ideal therapy for this condition would be an agent
which would regulate the serum lipid level as does estrogen, but would be devoid of the side-effects and risks associated
with estrogen therapy.

[0009] The third major pathology associated with post-menopausal syndrome is estrogen-dependent breast cancer
and, to a lesser extent, estrogen-dependent cancers of other organs, particularly the uterus. Although such neoplasms
are not solely limited to a post-menopausal women, they are more prevalent in the older, post-menopausal population.
Current chemotherapy of these cancers have relied heavily on the use of anti-estrogen compounds such as, for ex-
ample, Tamoxifen. Although such mixed agonist-antagonists have beneficial effects in the treatment of these cancers,
and the estrogenic side-effects are tolerable in acute life-threatening situations, they are not ideal. For example, these

agents may have stimulatory effects on certain cancer cell populations in the uterus due to their estrogenic (agonist) properties and they may, therefore, be contraproductive in some cases. A better therapy for the treatment of these cancers would be an agent which is an anti-estrogen compound having negligible or no estrogen agonist properties on reproductive tissues.

[0010] In response to the clear need for new pharmaceutical agents which are capable of alleviating the symptoms of, *inter alia*, post-menopausal syndrome, the present invention provides new benzothiofene compounds, pharmaceutical compositions thereof, and methods of using such compounds for the treatment of post-menopausal syndrome and other estrogen-related pathological conditions such as those mentioned below.

[0011] Uterine fibrosis is an old and ever present clinical problem which goes under a variety of names, including uterine hypertrophy, uterine leiomyomata, myometrial hypertrophy, fibrosis uteri, and fibrotic metritis. Essentially, uterine fibrosis is a condition where there is an inappropriate deposition of fibroid tissue on the wall of the uterus.

[0012] This condition is a cause of dysmenorrhea and infertility in women. The exact cause of this condition is poorly understood but evidence suggests that it is an inappropriate response of fibroid tissue to estrogen. Such a condition has been produced in rabbits by daily administrations of estrogen for 3 months. In guinea pigs, the condition has been produced by daily administration of estrogen for four months. Further, in rats, estrogen causes similar hypertrophy.

[0013] The most common treatment of uterine fibrosis involves surgical procedures both costly and sometimes a source of complications such as the formation of abdominal adhesions and infections. In some patients, initial surgery is only a temporary treatment and the fibroids regrow. In those cases a hysterectomy is performed which effectively ends the fibroids but also the reproductive life of the patient. Also, gonadotropin releasing hormone antagonists may be administered, yet their use is tempered by the fact they can lead to osteoporosis.

[0014] Endometriosis is a condition of severe dysmenorrhea, which is accompanied by severe pain, bleeding into the endometrial masses or peritoneal cavity and often leads to infertility. The cause of the symptoms of this condition appear to be ectopic endometrial growths which respond inappropriately to normal hormonal control and are located in inappropriate tissues. Because of the inappropriate locations for endometrial growth, the tissue seems to initiate local inflammatory-like responses causing macrophage infiltration and a cascade of events leading to initiation of the painful response. The exact etiology of this disease is not well understood and its treatment by hormonal therapy is diverse, poorly defined, and marked by numerous unwanted and perhaps dangerous side effects.

[0015] One of the treatments for this disease is the use of low dose estrogen to suppress endometrial growth through a negative feedback effect on central gonadotropin release and subsequent ovarian production of estrogen; however, it is sometimes necessary to use continuous estrogen to control the symptoms. This use of estrogen can often lead to undesirable side effects and even the risk of endometrial cancer.

[0016] Another treatment consists of continuous administration of progestins which induces amenorrhea and by suppressing ovarian estrogen production can cause regressions of the endometrial growths. The use of chronic progestin therapy is often accompanied by the unpleasant CNS side effects of progestins and often leads to infertility due to suppression of ovarian function.

[0017] A third treatment consists of the administration of weak androgens, which are effective in controlling the endometriosis; however, they induce severe masculinizing effects. Several of these treatments for endometriosis have also been implicated in causing a mild degree of bone loss with continued therapy. Therefore, new methods of treating endometriosis are desirable.

[0018] Aortal smooth muscle cell proliferation plays an important role in diseases such as atherosclerosis and restenosis. Vascular restenosis after percutaneous transluminal coronary angioplasty (PTCA) has been shown to be a tissue response characterized by an early and late phase. The early phase occurring hours to days after PTCA is due to thrombosis with some vasospasms while the late phase appears to be dominated by excessive proliferation and migration of aortal smooth muscle cells. In this disease, the increased cell motility and colonization by such muscle cells and macrophages contribute significantly to the pathogenesis of the disease. The excessive proliferation and migration of vascular aortal smooth muscle cells may be the primary mechanism to the reocclusion of coronary arteries following PTCA, atherectomy, laser angioplasty and arterial bypass graft surgery. See "Intimal Proliferation of Smooth Muscle Cells as an Explanation for Recurrent Coronary Artery Stenosis after Percutaneous Transluminal Coronary Angioplasty," Austin *et al.*, *Journal of the American College of Cardiology* 8: 369-375 (Aug. 1985).

[0019] Vascular restenosis remains a major long term complication following surgical intervention of blocked arteries by percutaneous transluminal coronary angioplasty (PTCA), atherectomy, laser angioplasty and arterial bypass graft surgery. In about 35% of the patients who undergo PTCA, reocclusion occurs within three to six months after the procedure. The current strategies for treating vascular restenosis include mechanical intervention by devices such as stents or pharmacologic therapies including heparin, low molecular weight heparin, coumarin, aspirin, fish oil, calcium antagonist, steroids, and prostacyclin. These strategies have failed to curb the reocclusion rate and have been ineffective for the treatment and prevention of vascular restenosis. See "Prevention of Restenosis after Percutaneous Transluminal Coronary Angioplasty: The Search for a 'Magic Bullet'", Hermans *et al.*, *American Heart Journal* 122: 171-187 (July 1991).

[0020] In the pathogenesis of restenosis excessive cell proliferation and migration occurs as a result of growth factors produced by cellular constituents in the blood and the damaged arterial vessel wall which mediate the proliferation of smooth muscle cells in vascular restenosis.

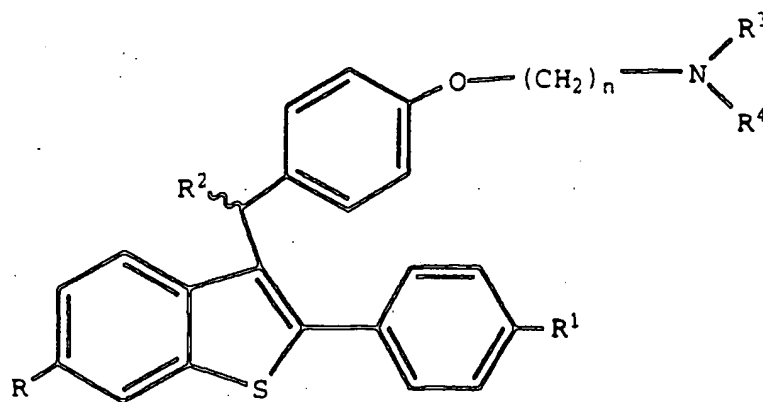
[0021] Agents that inhibit the proliferation and/or migration of aortal smooth muscle cells are useful in the treatment and prevention of restenosis. The present invention provides for the use of compounds as aortal smooth muscle cell proliferation inhibitors and, thus, inhibitors of restenosis.

[0022] WO-A-95/10513 describes benzothiophenes and related compounds, which are useful as estrogen agonists.

[0023] EP-A-O 062 503 discloses 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-{3-methylpyrrolidino}ethoxy)benzoyl]benzo[b]thiophene (and derivatives) and 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene (and derivatives) as valuable antiestrogens and antiandrogens

[0024] EP-A-0516257 discloses 2-phenylbenzo[b]furane and (2-phenylbenzo[b]thiophene) derivatives.

[0025] The present invention relates to compounds of formula 1



I

wherein

R is -H, -OH, -O(C₁-C₄ alkyl), -O-CO-(C₁-C₆ alkyl), -O-CO-Ar in which Ar is optionally substituted phenyl, or -O-SO₂-(C₄-C₆ alkyl);

R¹ is -H, -OH, -O(C₁-C₄ alkyl), -O-CO-(C₁-C₆ alkyl), -O-CO-Ar in which Ar is optionally substituted phenyl, or -O-SO₂-(C₄-C₆ alkyl), chloro or bromo;

R² is -H or -OH;

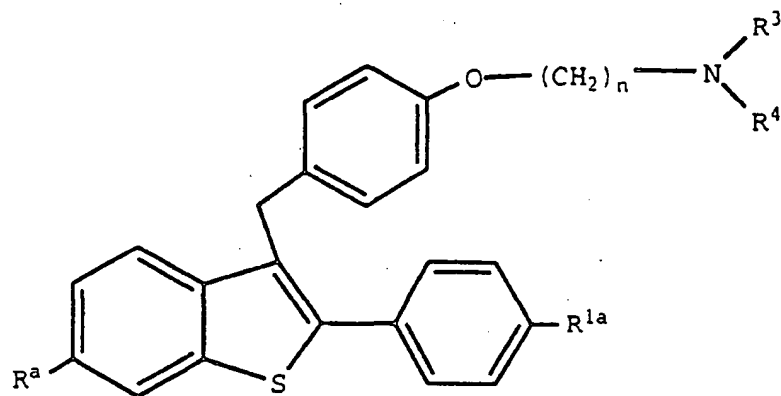
n is 2 or 3; and

R³ and R⁴ each independently C₁-C₄ alkyl, or combine to form 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, or 1-hexamethyleneimino; or a pharmaceutically acceptable salt thereof; other than the compound 2-(4-hydroxyphenyl)-3-[4-(2-piperidin-1-ylethoxy)-benzyl]benzo[b]thiophene-6-ol.

[0026] The present invention also relates to pharmaceutical compositions containing compounds of formula I, optionally containing estrogen or progestin, and the use of such compounds, alone, or in combination with estrogen or progestin, for alleviating the symptoms of post-menopausal symptoms, particularly osteoporosis, cardiovascular related pathological conditions, and estrogen-dependent cancer. As used herein, the term "progestin" includes compounds having progestational activity such as, for example, progesterone, norethynodrel, norgestrel, megestrol acetate, norethindrone, and the like.

[0027] The present invention further relates to the use of the compounds of the present invention for inhibiting uterine fibroid disease and endometriosis in women and aortal smooth muscle cell proliferation, particularly restenosis, in humans.

[0028] Furthermore, the present invention relates to a process for preparing a compound of formula Ic



Ic

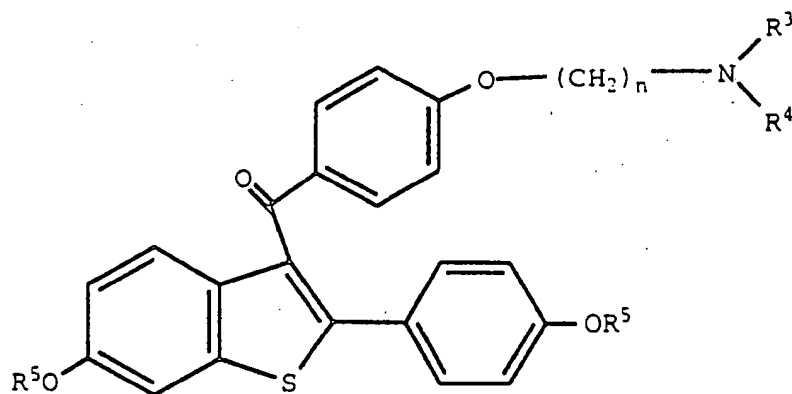
wherein

R^a and R^{1a} each are $-OH$ or $-OR^5$;

R^3 and R^4 each are independently C_1 - C_4 alkyl, or combine to form 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, or 1-hexamethyleneimino; and

R^5 is a hydroxy protecting group capable of resisting reduction by a strong reducing agent; or a pharmaceutically acceptable salt thereof, which comprises

a) optionally removing the R^5 hydroxy protecting groups of a compound of formula II



II

wherein

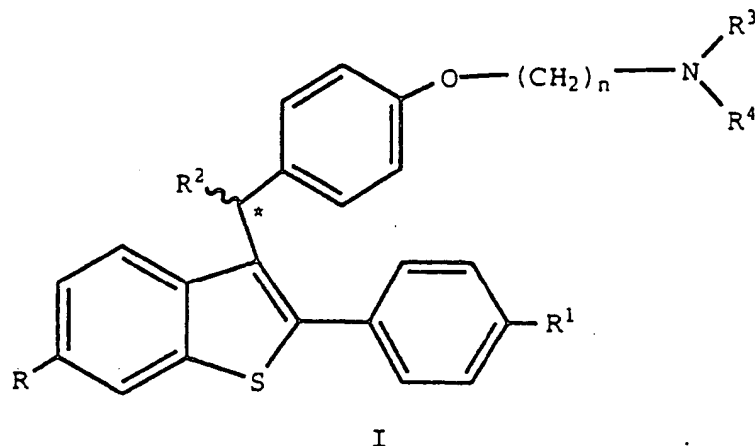
n , R^3 , R^4 , and R^5 are as defined above, or a salt thereof;

b) reacting said formula II compound with a reducing agent in the presence of a solvent having a boiling point in the range from about $150^\circ C$ to about $200^\circ C$, and heating the mixture to reflux; and

c) optionally salifying the reaction product from step b).

Detailed Description of the Invention

[0029] One aspect of the present invention includes compounds of formula I



wherein

R is -H, -OH, -O(C₁-C₄ alkyl), -O-CO-(C₁-C₆ alkyl), -O-CO-Ar in which Ar is optionally substituted phenyl, or -O-SO₂-(C₄-C₈ alkyl);

R¹ is -H, -OH, -O(C₁-C₄ alkyl), -O-CO-(C₁-C₆ alkyl), -O-CO-Ar in which Ar is optionally substituted phenyl, -O-SO₂-(C₄-C₈ alkyl), chloro or bromo;

R² is -H or -OH;

n is 2 or 3; and

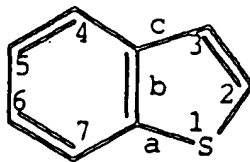
R³ and R⁴ each are independently C₁-C₄ alkyl, or combine to form 1-piperidinyl, 1-pyrrolidinyl, methyl-1-piperidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, 1-hexamethyleneimino; or a pharmaceutically acceptable salt thereof.

[0030] In formula I, when R² is -OH, the carbon atom designated "*" is an asymmetric center. Thus, such compounds of formula I can have an R- or S-configuration, or a mixture thereof.

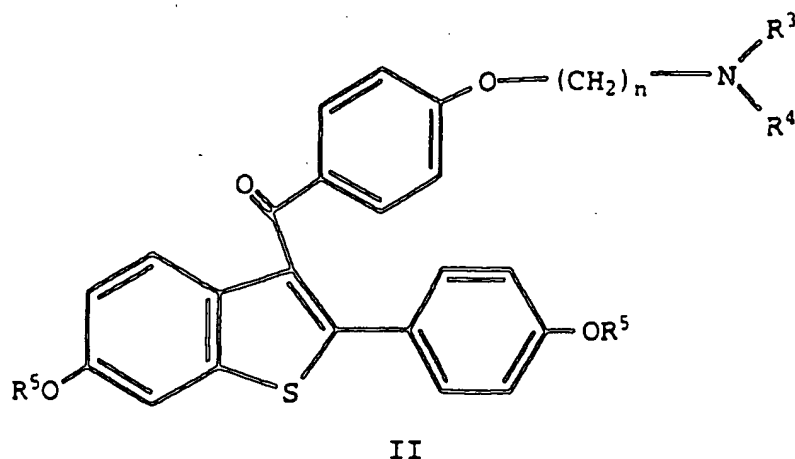
[0031] General terms used in the description of formula I compounds bear their usual meanings. For example, "C₁-C₄ alkyl" refers to straight or branched aliphatic chains of 1 to 4 carbon atoms including methyl, ethyl, propyl, isopropyl, butyl, n-butyl, and the like; and "C₁-C₆ alkyl" encompasses the groups included in the definition of "C₁-C₄ alkyl" in addition to groups such as pentyl, isopentyl, hexyl, isohexyl, and the like.

[0032] The term "substituted phenyl" refers to a phenyl group having one or more substituents selected from the group consisting of C₁-C₄ alkyl, C₁-C₅ alkoxy, hydroxy, nitro, chloro, fluoro, or tri(chloro or fluoro)methyl. "C₁-C₅ alkoxy" represents a C₁-C₅ alkyl group attached through an oxygen bridge such as, for example, methoxy, ethoxy, n-propoxy, isopropoxy, and the like.

[0033] The compounds of the present invention are derivatives of benzo[b]thiophene which is named and numbered according to the Ring Index, The American Chemical Society, as follows



[0034] In the processes for preparing the compounds of the present invention, the starting material is a compound of formula II

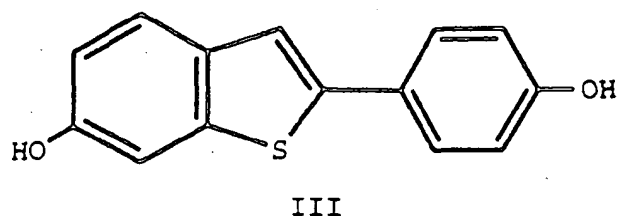


wherein

R⁵ is a hydroxy protecting group capable of resisting reduction by a strong reducing agent; and
n, R³ and R⁴ are as defined above; or a salt thereof.

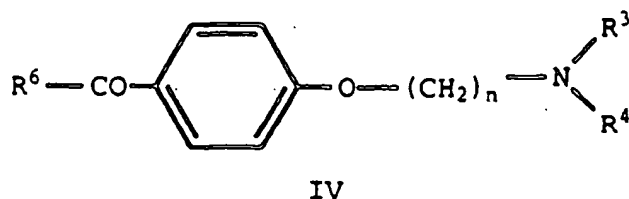
[0035] Although the free base of a formula II compound is an acceptable starting material, an acid addition salt form, particularly the hydrochloride salt, is often more convenient.

[0036] Compounds of formula II are known in the art and essentially are prepared via the methods described in U. S. Pat. Nos. 4,133,814; 4,380,635; and 4,418,068. Generally, a benzothiophene precursor of formula III



is prepared via known procedures. Typically, the two hydroxy groups are protected by known hydroxy protecting groups which are capable of resisting acylation under standard Fiedel-Crafts conditions (forming the R⁵ protecting groups of formula II compounds) and subsequent reduction by a strong reducing agent. Preferred hydroxy protecting groups are C₁-C₄ alkyl, and methyl is especially preferred. See, e.g., the aforementioned United States patents, J. W. Barton, "Protective Groups in Organic Chemistry", J. G. W. McOmie (ed.), Plenum Press, New York, NY, 1973, Chapter 2, and T. W. Green, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1981, Chapter 7.

[0037] Following preparation of the desired protected formula III precursor, the precursor is acylated, using standard Friedel-Crafts conditions, with a compound of formula IV



wherein

n, R³, and R⁴ are as defined above; and

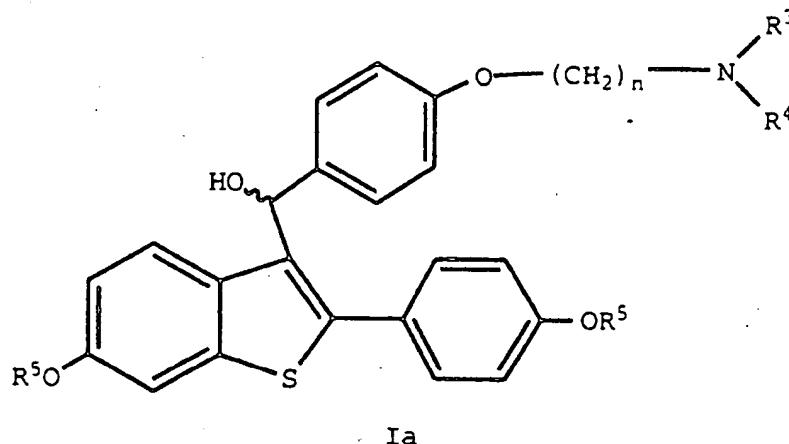
R⁶ is chloro, bromo, iodo, or an activating ester group. Preparation of formula IV compounds, as well as preferred acylation methods, are disclosed in the aforementioned

[0038] United States patents. When R^3 and R^4 each are C_1 - C_4 alkyl, methyl and ethyl are preferred. When R^3 and R^4 are combined, 1-piperidinyl and 1-pyrrolidinyl are preferred. Of these, the piperidino moiety is especially preferred.

[0039] Following acylation and, thus, preparation of a compound of formula II, compounds of the present invention in which R^2 is -OH are prepared by adding a formula II compound or a salt thereof, to an appropriate solvent, and then reacting the formula II compound with a reducing agent such as, for example, lithium aluminum hydride (LAH), under an inert gas such as nitrogen.

[0040] Although the free base of a formula II compound may be used in this reaction, an acid addition salt, preferably the hydrochloride salt, is often more convenient.

[0041] The amount of reducing agent used in this reaction is an amount sufficient to reduce the carbonyl group of formula II to form a carbinol of formula Ia. Generally, a liberal excess of the reducing agent per equivalent of the substrate is used.



wherein n , R^3 , R^4 and R^5 are as defined above, or a salt thereof.

[0042] Appropriate solvents include any solvent or mixture of solvents which will remain inert under reducing conditions. Suitable solvents include diethyl ether, dioxane, and tetrahydrofuran (THF). The anhydrous form of these solvents is preferred, and anhydrous THF is especially preferred.

[0043] The temperature employed in this step is that which is sufficient to effect completion of the reduction reaction. Ambient temperature, in the range from about 17° C to about 25° C, generally is adequate.

[0044] The length of time for this step is that amount necessary for the reaction to occur. Typically, this reaction takes from about 1 to about 20 hours. The optimal time can be determined by monitoring the progress of the reaction via conventional chromatographic techniques.

[0045] The carbinol products from this reaction are extracted essentially via the method described in Example 1, *infra*, are novel, and are useful for the methods described herein.

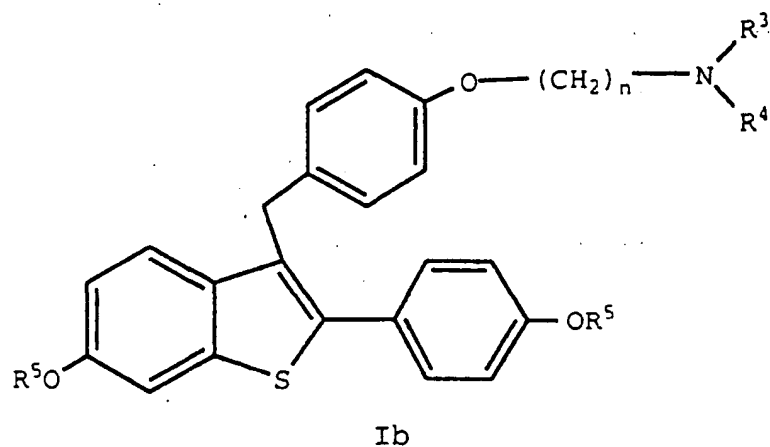
[0046] Once a carbinol of the present invention is prepared, one option is to further reduce such a carbinol via standard procedures, to give a compound of formula I in which R^2 is H.

[0047] Typically, a carbinol of formula I is suspended in an appropriate solvent and cooled under an inert gas such as nitrogen. To this suspension is added a suitable trialkyl silane reducing agent, preferably triethyl silyl, and a reasonably strong protic acid such as hydrochloric acid, trifluoroacetic acid, and the like.

[0048] Appropriate solvents can be any solvent or mixture of solvents which remain inert under the reaction conditions employed in the process. For example, halogenated alkane solvents such as dichloromethane and 1,2-dichloroethane, as well as haloaromatics such as chlorobenzene and the like may be used. Of these, dichloromethane is preferred.

[0049] The temperature employed in this step is that which is sufficient to effect completion of the present reduction process. Typically, the reaction is cooled to about 0° C and the reaction solution is kept on ice until the reaction is complete; however, ambient temperature also is satisfactory. In general, this reaction is completed in less than three hours, and the progress of the reaction can be monitored via standard techniques.

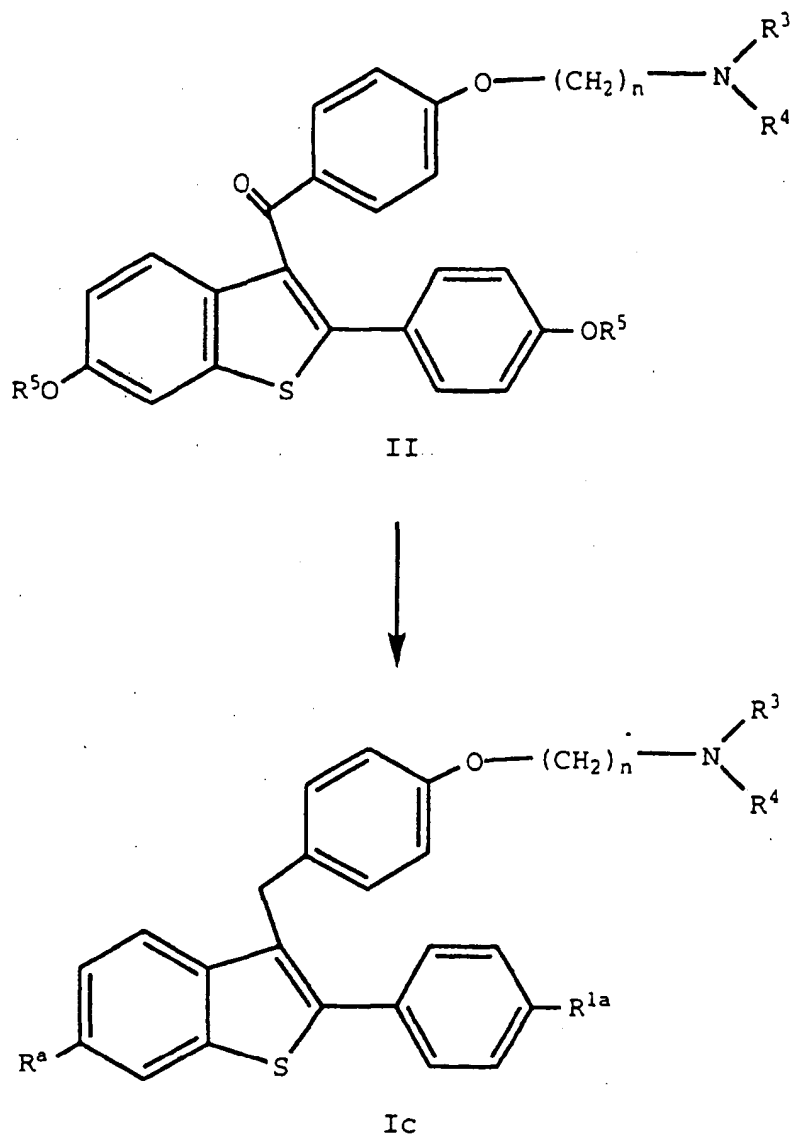
[0050] The product of this reaction, a formula Ib compound, is extracted and purified via standard techniques, especially via the procedure described in Example 2, *infra*. The compounds prepared by this process also are novel and useful for the methods herein described.



wherein n, R³, R⁴, and R⁵ are as defined above, or a salt thereof.

[0051] Alternatively, a novel process may be used to prepare formula Ic compounds of the present invention by
20 reducing a ketone of formula II above. This process is shown in Scheme I below.

Scheme I



wherein

R^a and R^{1a} each are -OH or -OR⁵; and

R^3 , R^4 , R^5 , and n are as defined above; or a pharmaceutically acceptable salt thereof.

[0052] In this process, the R^5 hydroxy protecting groups of a formula II compound, in which R^5 preferably is methyl, optionally are removed, and the protected or deprotected compound is reacted with a reducing agent such as lithium aluminum hydride in the presence of an inert solvent having a boiling point in the range from about 150° C to about 200° C. The reaction product from this reduction step can then optionally be salified via standard procedures. Preferably, each step of this novel process is carried out in separate vessels, it is possible to carry out each step of the present process in the same vessel.

[0053] The amount of reducing agent used in this reaction is an amount sufficient to reduce the carbonyl group of a formula II compound to form a compound of formula Ic. Generally, a substantial excess of the reducing agent per equivalent of the substrate is used.

[0054] The solvent used in the present process is required to have a relatively high boiling point, in the range from about 150° C to about 200° C, as represented by solvents such as, for example, n-propylbenzene, diglyme (1,1'-oxybis[2-methoxyethane]), and anisole, and Red-AK® ([sodium bis(2-methoxyethoxyaluminum hydride)]) which also is used

as the reducing agent. When the R^5 substituents of formula II compounds are hydroxy protecting groups, n-propylbenzene is the preferred solvent. When such R^5 protecting groups are first optionally removed prior to reduction, Red-Al is the preferred reagent.

[0055] The temperature used in this reaction is that which is sufficient to complete the reduction reaction. Preferably, the reaction mixture is heated to reflux for about 15 minutes to about 6 hours, and allowed to cool to ambient temperature. When R^a and R^{1a} are $-OR^5$, a small amount of deionized water is added to the mixture followed by the addition of a small aliquot of 15% sodium hydroxide:deionized water (w/w). When R^a and R^{1a} are $-OH$, the reaction is carefully quenched with excess 1.0 N hydrochloric acid. The optimal amount of time for these reactions to run, typically from about 10 minutes to about 3 hours, can be determined by monitoring the progress of the reaction via standard techniques.

[0056] The formula Ic products from this reduction reaction are extracted essentially as described in Example 22 or 23.

[0057] Formula Ia and Ib compounds, in which R^2 is $-H$ or $-OH$ as described above, or formula Ic compounds in which R^a and R^{1a} each are $-OR^5$ and R^5 , is as defined above, can be used for the methods of the present invention, or the hydroxy protecting groups which are capable of resisting reduction are removed via procedures well known to one of ordinary skill in the art to provide preferred formula I compounds of the present invention in which R and R^1 each are $-OH$.

[0058] Other preferred compounds are prepared by replacing the newly formed R and R^1 hydroxy groups with a moiety of the formula $-O-CO-(C_1-C_6 \text{ alkyl})$, $-O-CO-Ar$ in which Ar is optionally substituted phenyl, or $-O-SO_2-(C_4-C_6 \text{ alkyl})$ via well known procedures. See, e.g., U.S. Pat. No. 4,358,593, *supra*.

[0059] For example, when a $-O-CO-(C_1-C_6 \text{ alkyl})$ or $-O-CO-Ar$ group is desired, the dihydroxy compound of formula I is reacted with an agent such as acyl chloride, bromide, cyanide, or azide, or with an appropriate anhydride or mixed with anhydride. The reactions are conveniently carried out in a basic solvent such as pyridine, lutidine, quinoline or isoquinoline, or in a tertiary amine solvent such as triethylamine, tributylamine, methylpiperidine, and the like. The reaction also may be carried out in an inert solvent such as ethyl acetate, dimethylformamide, dimethylsulfoxide, dioxane, dimethoxyethane, acetonitrile, acetone, methyl ethyl ketone, and the like, to which at least one equivalent of an acid scavenger, such as a tertiary amine, has been added. If desired, acylation catalysts such as 4-dimethylaminopyridine or 4-pyrrolidinopyridine may be used. See, e.g., Haslam, *et al.*, *Tetrahedron*, 36:2409-2433 (1980).

[0060] The acylation reactions which provide the aforementioned R and R^1 groups are carried out at moderate temperatures in the range from about -25°C to about 100°C , frequently under an inert atmosphere such as nitrogen gas. However, ambient temperature is usually adequate for the reaction to run.

[0061] Such acylations of the hydroxy group also may be performed by acid-catalyzed reactions of the appropriate carboxylic acids in inert organic solvents or heat. Acid catalysts such as sulfuric acid, polyphosphoric acid, methanesulfonic acid, and the like are used.

[0062] The aforementioned R and R^1 groups also may be provided by forming an active ester of the appropriate acid, such as the esters formed by such known reagents such as dicyclohexylcarbodiimide, acylimidazoles, nitrophenols, pentachlorophenol, N-hydroxysuccinimide, and 1-hydroxybenzotriazole. See, e.g., *Bull. Chem. Soc. Japan*, 38: 1979 (1965), and *Chem. Ber.*, 788 and 2024 (1970).

[0063] Each of the above techniques which provide $-O-CO-(C_1-C_6 \text{ alkyl})$ and $-O-CO-Ar$ groups are carried out in solvents as discussed above. These techniques which do not produce an acid product in the course of the reaction, of course, do not necessitate the use of an acid scavenger in the reaction mixture.

[0064] When a formula I compound is desired in which R and R^1 is $-O-SO_2-(C_4-C_6 \text{ alkyl})$, the formula I dihydroxy compound is reacted with, for example, a derivative of the appropriate sulfonic acid such as a sulfonyl chloride, bromide, or sulfonyl ammonium salt, as taught by King and Monoir, *J. Am. Chem. Soc.*, 97:2566-2567 (1975). The dihydroxy compound also can be reacted with the appropriate sulfonic anhydride. Such reactions are carried out under conditions such as were explained above in the discussion of reaction with acid halides and the like.

[0065] Compounds of formula I can be prepared so that R and R^1 bear different biological protecting groups or, preferably, are prepared so that R and R^1 each bear the same biological protecting group. Preferred protecting groups include $-OCH_3$, $-O-CO-C(CH_3)_3$, $-O-CO-C_6H_5$, and $-O-SO_2-(CH_2)_3-CH_3$.

[0066] The term "biological protecting groups" refers to those R and R^1 substituents which delay, resist, or prohibit removal of such groups in a biological system such as, for example, following administration of a formula I compound containing the above-described R and R^1 groups to a human. Such compounds of formula I also are useful for the methods herein described, especially when R^2 is $-H$.

[0067] Although the free-base form of formula I compounds can be used in the methods of the present invention, it is preferred to prepare and use a pharmaceutically acceptable salt form. Thus, the compounds used in the methods of this invention primarily form pharmaceutically acceptable acid addition salts with a wide variety of organic and inorganic acids, and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic,

hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric, and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, β -hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, terephthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzenesulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethane-sulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like. A preferred salt is the hydrochloride salt.

[0068] The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or ethyl acetate. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

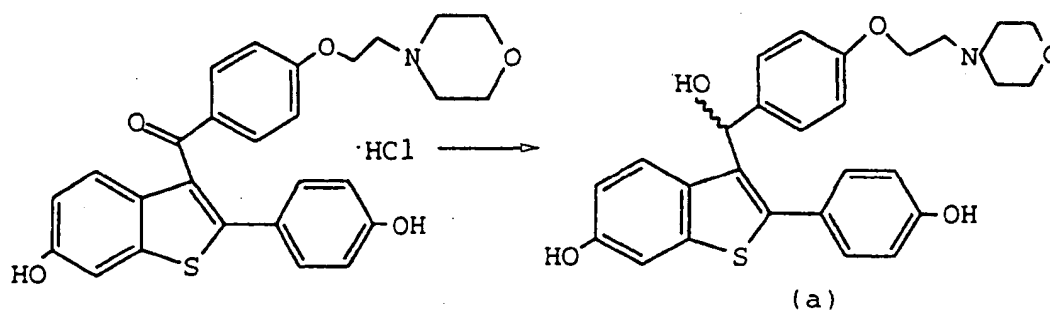
[0069] The pharmaceutically acceptable salts generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

[0070] The following examples are presented to further illustrate the preparation of compounds of the present invention. It is not intended that the invention be limited in scope by reason of any of the following examples.

[0071] NMR data for the following Examples were generated on a GE 300 MHz NMR instrument, and anhydrous d-6 DMSO was used as the solvent unless otherwise indicated.

Example 1

[6-HYDROXY-2-(4-HYDROXYPHENYL)BENZO[b]THIEN-3-YL][4-[2-(1-MORPHOLINO)ETHOXY]PHENYL] METHANOL



[0073] To 150 mL of anhydrous tetrahydrofuran (THF) was suspended 1.25 g of [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-morpholino)ethoxy]phenyl]methanone hydrochloride under nitrogen gas and at ambient temperature. To this suspension was added 0.56 g of lithium aluminum hydride portionwise over 30 minutes and then allowed to stir for 16 hours at ambient temperature. The mixture was quenched by pouring it into ethyl acetate, and the solvent was concentrated to provide a gray solid material. This solid was suspended in a mixture of 30 mL of methanol, 100 mL of saturated sodium bicarbonate, and 200 mL of ethyl acetate. The aqueous phase was extracted several times with ethyl acetate. The organic extracts were combined, dried on sodium sulfate, and the solvent concentrated off to yield 1.1 g of a light yellow foam. ¹H NMR(d₆-DMSO); (2.5ppm, 4H, broad peak, NCH₂CH₂O); (2.7ppm, 2H, triplet, PhOCH₂CH₂N); (3.4ppm, 4H, broad peak, NCH₂CH₂O); (4.1ppm, 2H, triplet, PhOCH₂CH₂N); (6.0ppm, 2H, broad singlet, benzylOH and H); (6.65ppm, 2H, dd, J=.03, position 5); (6.85ppm, 4H, complex, 2' and 3' position); (7.25ppm, 1H, singlet, position 7); (7.25ppm, 2H, doublet, J=.03, 3" position); (7.45ppm, 2H, doublet, J=.03, 2" position); (7.55ppm, 1H, doublet, J=.03, position 4); (9.55ppm, 1H, broad singlet, phenol); (9.8ppm, 1H, broad singlet, phenol). MS(FD) m/z 478 (M⁺); Anal. Calcd. for: C, 67.91; H, 5.70; N, 2.93. Found: C, 67.82; H, 5.96; N, 2.99.

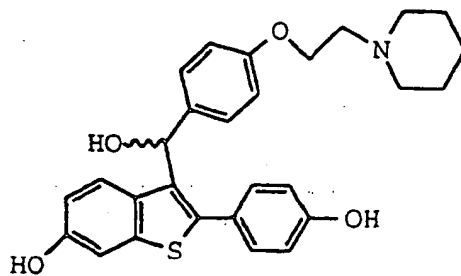
[0074] By following the procedure described in Example 1, and employing the proper reactants, Examples 2 through

9 were prepared.

Example 2

[6-HYDROXY-2-(4-HYDROXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(1-PIPERIDINYL)ETHOXY]PHENYL]
METHANOL

[0075]



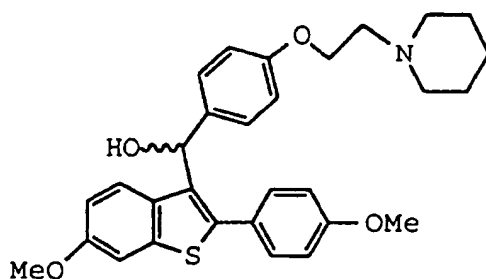
(b)

¹H NMR(d₆-DMSO); (1.4ppm, 2H, broad peak, NCH₂CH₂CH₂); (1.55ppm, 4H, broad peak, NCH₂CH₂); (2.45ppm, 4H, broad peak, OCH₂CH₂NCH₂); (2.65ppm, 2H, triplet, OCH₂CH₂N); (4.05ppm, 2H, triplet, PhOCH₂CH₂); (6.0ppm, 2H, broad singlet, benzylOH and H); (6.9ppm, 4H, complex, 2' and 3' position); (7.25ppm, 1H, singlet, position 7); (7.25ppm, 2H, doublet, J=.03, 3" position); (7.4ppm, 2H, doublet, J=.03, 2" position); (7.55ppm, 1H, doublet, J=.03, position 4); (9.55ppm, 1H, broad singlet, phenol); (9.8ppm, 1H, broad singlet, phenol). MS(FD) m/z 476 (M⁺).

Example 3

[6-METHOXY-2-(4-METHOXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(1-PIPERIDINYL)ETHOXY]PHENYL]
METHANOL

[0076]



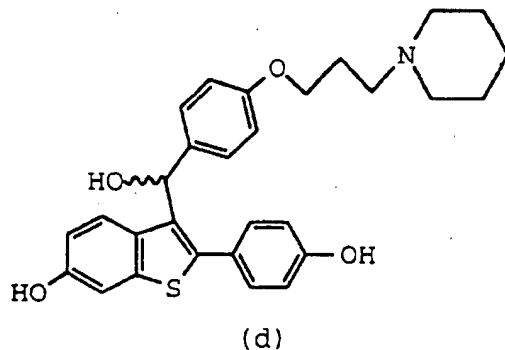
(c)

¹H NMR(d₆-DMSO); (1.35ppm, 2H, broad peak, NCH₂CH₂CH₂); (1.45ppm, 4H, broad peak, NCH₂CH₂); (2.4ppm, 4H, broad peak, CH₂NCH₂); (2.6ppm, 2H, triplet, OCH₂CH₂N); (3.8ppm, 6H, singlet, OMe); (4.0ppm, 2H, triplet, PhOCH₂CH₂N); (5.95ppm, 1H, singlet, benzylH); (6.05ppm, 1H, singlet, benzylOH); (6.8ppm, 3H, doublet, J=.03, 3' and 5 position); (7.05ppm, 2H, doublet, J=.03, 2' position); (7.15ppm, 2H, doublet, J=.03, 3" position); (7.50ppm, 1H, singlet, 7 position); (7.50ppm, 2H, doublet, J=.03, 2" position); (7.6ppm, 1H, doublet, J=.03, position 4). MS(FD) m/z 503 (M⁺).

Example 4

[6-HYDROXY-2-(4-HYDROXYPHENYL)BENZO[B]THIEN-3-YL][4-[3-(1-PIPERIDINYL)PROPOXY]PHENYL] METHANOL

[0077]

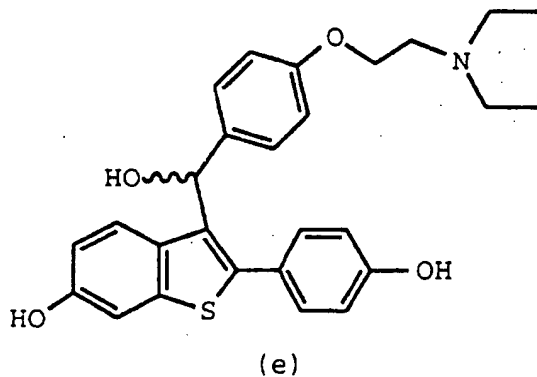


¹H NMR(d₆-DMSO); (1.4ppm, 2H, broad peak, NCH₂CH₂CH₂); (1.55ppm, 4H, broad peak, NCH₂CH₂CH₂); (1.9ppm, 2H, multiplet, PhOCH₂CH₂CH₂); (2.35ppm, 4H, broad peak, NCH₂CH₂CH₂); (2.4ppm, 2H, triplet, PhOCH₂CH₂CH₂); (4.0ppm, 2H, triplet, PhOCH₂CH₂); (6.0ppm, 2H, broad singlet, benzyloH and H); (6.65ppm, 1H, dd, J=.03, position 5); (6.85ppm, 4H, complex, 2'and 3' position); (7.15ppm, 1H, singlet, position 7); (7.15ppm, 2H, doublet, J=.03, 3" position); (7.35ppm, 2H, doublet, J=.03, 2" position); (7.45ppm, 1H, doublet, J=.03, position 4); (9.65ppm, 2H, broad peak, phenols). MS(FD) m/z 490 (M+).

Example 5

[6-HYDROXY-2-(4-HYDROXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(1-PYRROLIDINYL)ETHOXY]PHENYL] METHANOL

[0078]

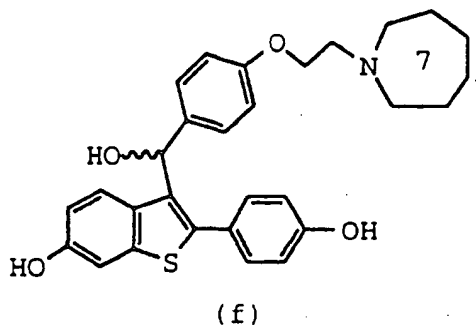


¹H NMR(d₆-DMSO); (1.65ppm, 4H, broad peak, NCH₂CH₂); (2.5ppm, 4H, broad peak, OCH₂CHNCH₂); (2.75ppm, 2H, triplet, OCH₂CH₂N); (4.0ppm, 2H, triplet, PhOCH₂CH₂); (5.95ppm, 2H, broad singlet, benzyloH and H); (6.65, 1H, dd, J=.03, position 5); (6.85ppm, 4H, complex, 2'and 3' position); (7.15ppm, 1H, singlet, position 7); (7.15ppm, 2H, doublet, J=.03, 3" position); (7.35ppm, 2H, doublet, J=.03, 2" position); (7.45ppm, 1H, doublet, J=.03, position 4); (9.45ppm, 1H, singlet, phenol); (9.70ppm, 1H, singlet, phenol). MS(FD) m/z 490 (M+).

Example 6

[6-HYDROXY-2-(4-HYDROXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(1-HEXAMETHYLENEIMINYL)ETHOXY]PHENYL]METHANOL

[0079]

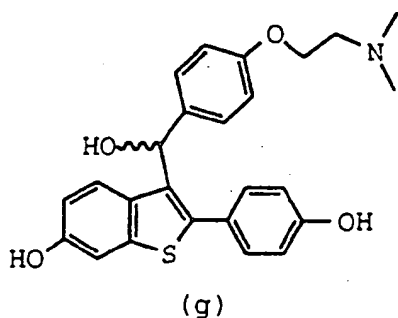


¹H NMR(d₆-DMSO); (1.5ppm, 4H, broad peak, NCH₂CH₂CH₂); (2.65ppm 4H, broad peak, NCH₂CH₂); (2.8ppm, 2H, triplet, PhOCH₂CH₂); (3.35ppm, 4H, broad peak, NCH₂); (3.95ppm, 2H, triplet, PhOCH₂CH₂); (5.95ppm, 2H, broad singlet, PhOH and H); (6.65ppm, 1H, dd, J=.03, position 5); (6.85ppm, 4H, complex, 2' and 3' position); (7.15ppm, 2H, doublet, J=.03, 3" position); (7.15ppm, 1H, singlet, position 7); (7.35ppm, 2H, doublet, J=.03, 2" position); (7.5ppm, 1H, doublet, J=.03, position 4); (9.5ppm, 1H, broad singlet, phenol); (9.7ppm, 1H, broad singlet, phenol). MS(FD) m/z 490 (M⁺).

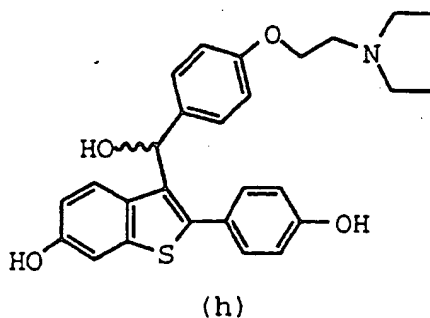
Example 7

[6-HYDROXY-2-(4-HYDROXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(N,N-DIMETHYLAMINO)ETHOXY]PHENYL]METHANOL

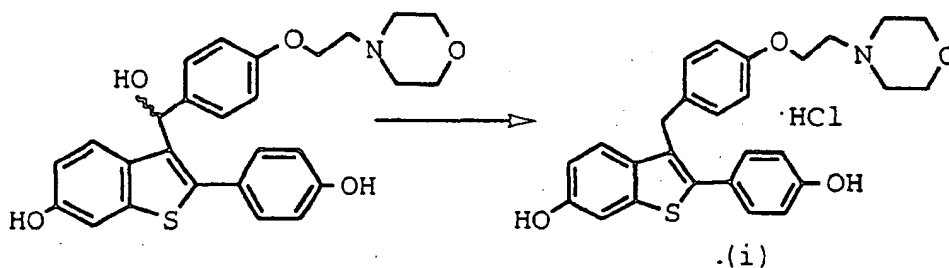
[0080]



¹H NMR(d₆-DMSO); (2.2ppm, 6H, singlet, N(CH₃)₂); (2.55ppm, 2H, triplet, OCH₂CH₂N(CH₃)₂); (3.95ppm, 2H, triplet, PhOCH₂CH₂N); (5.95ppm, 2H, broad singlet, benzylOH and H); (6.65ppm, 1H, dd, J=.03, position 5); (6.85ppm, 4H, complex, 2' and 3' position); (7.2ppm, 1H, singlet, position 7); (7.2ppm, 2H, doublet, J=.03, 3" position); (7.35ppm, 2H, doublet, J=.03, 2" position); (7.5ppm, 1H, doublet, J=.03, position 4); (9.5ppm, 1H, broad singlet, phenol); (9.7ppm, 1H, broad singlet, phenol). MS(FD) m/z 436 (M⁺).

Example 8**[6-HYDROXY-2-(4-HYDROXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(N,N-DIETHYLAMINO)ETHOXY]PHENYL] METHANOL****[0081]**

¹H NMR(d₆-DMSO); (1.0ppm, 6H, triplet, NCH₂CH₃); (2.6ppm, 4H, quartet, NCH₂CH₃); (2.8ppm, 2H, triplet, PhOCH₂CH₂N); (4.0ppm, 2H, triplet, PhOCH₂CH₂N); (6.0ppm, 2H, broad peak, benzylOH and H); (6.7ppm, 1H, dd, J=.03, position 5); (7.85ppm, 4H, complex, 2' and 3' position); (7.2ppm, 1H, singlet, position 7); (7.2ppm, 2H, doublet, J=.03, 3" position); (7.4ppm, 2H, doublet, J=.03, 2" position); (7.5ppm, 1H, doublet, J=.03, position 4); (9.7ppm, 2H, broad peak, phenols). MS(FD) m/z 464 (M⁺).

Example 9**[6-HYDROXY-2-(4-HYDROXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(N,N-MORPHOLINO)ETHOXY]PHENYL] METHANE HYDROCHLORIDE****[0082]**

[0083] In 50 mL of dichloromethane (DCM) was suspended the product from Example 1, and cooled to 0° C on an ice bath. To this suspension was added 1.6 g of triethyl silane and the mixture was stirred for 10 minutes. Then, 15 mL of trifluoroacetic acid was added dropwise at a rate so as to keep the temperature below about 5° C and the mixture was stirred on an ice bath, under nitrogen gas, for 2 hours. The reaction was quenched by pouring the mixture into cold DCM (about 100 mL) and sodium bicarbonate (about 75 mL). The resulting gum was redissolved by adding a few milliliters of methanol or DCM. The organic phase was washed several times with saturated sodium bicarbonate solution and once with deionized water. The organic phase was dried on sodium sulfate and concentrated to yield a clear, light yellow gum which was taken up in acetone. To the acetone solution was added a saturated solution of hydrogen chloride gas in acetone until a precipitate formed. The acetone was removed under vacuum and the resulting gum was triturated extensively in diethyl ether. The resulting solid was collected and recrystallized from a mixture of methanol and ethyl ether to yield 650 mg of a white granular product. ¹H NMR(d₆-DMSO); (3.2ppm, 2H, broad peak, CH₂NCH₂CH₂O); (3.4ppm, 4H, broad peak, CH₂NCH₂CH₂O); (3.75ppm, 2H, broad peak, NCH₂CH₂O); (3.95ppm, 2H, broad peak, NCH₂CH₂O); (4.10ppm, 2H, singlet, benzylCH₂); (4.3ppm, 2H, triplet, PhOCH₂CH₂); (6.8ppm, 1H, dd, J=.03, position 5); (6.9ppm, 4H, complex, 3' and 2'); (7.05, 1H, doublet, J=.03, position 4); (7.05ppm, 1H, singlet, position 7); (7.3ppm,

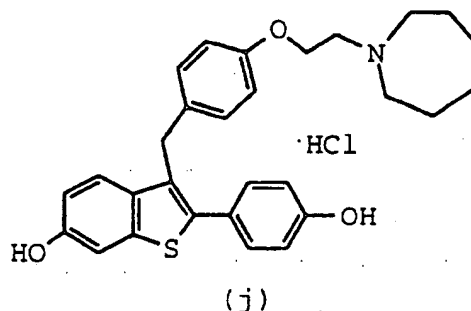
4H, complex, 3" and 2"); (9.6ppm, 1H, singlet, phenol); (9.75ppm, 1H, singlet, phenol); (10.75ppm, 1H, broad peak, HCl). MS(FD) m/z 461 (M+-HCl); Anal. Calcd. for: C, 65.12; H, 5.62; N, 2.81. Found: C, 64.99; H, 5.62; N, 2.86.

[0084] By following the procedures described in Example 9, and employing the proper reactants, Examples 10 through 15 were prepared.

Example 10

[6-HYDROXY-2-(4-HYDROXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(1-HEXAMETHYLENEIMINYL)ETHOXY]PHENYL]METHANE HYDROCHLORIDE

[0085]

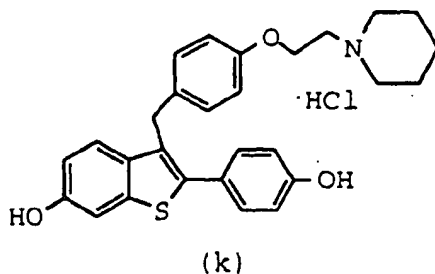


¹H NMR(d₆-DMSO); (1.6ppm, 4H, broad peak, NCH₂CH₂CH₂CH₂); (1.8ppm, 4H, broad peak, NCH₂CH₂CH₂CH₂CH₂CH₂); (3.2ppm, 2H, broad peak, CH₂NCH₂); (3.4ppm, 4H, broad peak, CH₂NCH₂); (4.1ppm, 2H, singlet, benzylCH₂); (4.3ppm, 2H, triplet, PhOCH₂CH₂); (6.8ppm, 1H, dd, J=.03, position 5); (6.9ppm, 4H, complex, 3' and 2"); (7.05ppm, 1H, doublet, J=.03, position 4); (7.05ppm, 1H, singlet, position 7); (7.3ppm, 4H, complex, 3" and 2"); (9.6ppm, 1H, singlet, phenol); (9.75ppm, 1H, singlet, phenol); (10.3ppm, 1H, broad peak, HCl). MS(FD) m/z 474 (M+-HCl); Anal. Calcd. for: C, 68.29; H, 6.32; N, 2.75. Found: C, 68.05; H, 6.28; N, 2.84.

Example 11

[6-HYDROXY-2-(4-HYDROXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(1-PIPERIDINYL)ETHOXY]PHENYL]METHANE HYDROCHLORIDE

[0086]

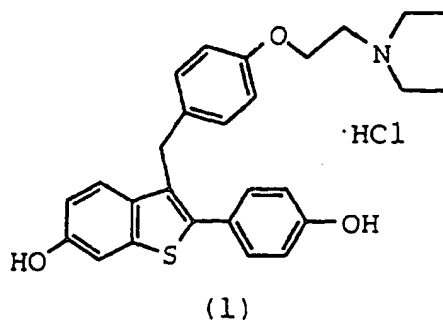


¹H NMR(d₆-DMSO); (1.4ppm, 2H, broad peak, NCH₂CH₂CH₂); (1.75ppm, 4H, broad peak, NCH₂CH₂); (2.95ppm, 2H, broad peak, CH₂NCH₂); (3.4ppm, 4H, broad peak, CH₂NCH₂); (4.1ppm, 2H, singlet, benzylCH₂); (4.3ppm, 2H, triplet, PhOCH₂); (6.8ppm, 1H, dd, J=.03, position 5); (6.9ppm, 4H, complex, 3'and 2"); (7.05ppm, 1H, doublet, J=.03, position 4); (7.05ppm, 1H, singlet, position 7); (7.3ppm, 4H, complex, 3"and 2"); (9.6ppm, 1H, singlet, phenol); (9.75ppm, 1H, singlet, phenol); (10.25ppm, 1H, broad peak, HCl). MS(FD) m/z 460 (M+-HCl); Anal. Calcd. For: C, 67.80; H, 6.20; N, 2.82. Found: C, 67.64; H, 6.29; N, 2.77.

Example 12

**[6-HYDROXY-2-(4-HYDROXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(1-PYRROLIDINYL)ETHOXY]PHENYL]
METHANE HYDROCHLORIDE**

[0087]

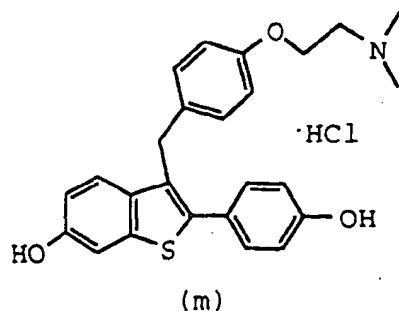


¹H NMR(d₆-DMSO); (1.85ppm, 2H, broad peak, NCH₂CH₂); (1.95ppm, 2H, broad peak, NCH₂CH₂); (3.05ppm, 2H, broad peak, CH₂NCH₂); (3.55ppm, 4H, broad peak, CH₂NCH₂); (4.1ppm, 2H, singlet, benzylCH₂); (4.25ppm, 2H, triplet, PhOCH₂CH₂); (6.8ppm, 1H, dd, J=.03, position 5); (6.9ppm, 4H, complex, 3' and 2'); (7.05ppm, 1H, doublet, J=.03, position 4); (7.05ppm, 1H, singlet, position 7); (7.3ppm, 4H, complex, 3" and 2"); (9.6ppm, 1H, singlet, phenol); (9.75ppm, 1H, singlet, phenol); (10.55ppm, 1H, broad peak, HCl). MS(FD) m/z 446 (M⁺-HCl); Anal. Calcd. for: C, 67.28; H, 5.86; N, 2.91. Found: C, 66.99; H, 5.86; N, 2.85.

Example 13

**[6-HYDROXY-2-(4-HYDROXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(N,N-DIMETHYLAMINO)ETHOXY]PHENYL]
METHANE HYDROCHLORIDE**

[0088]

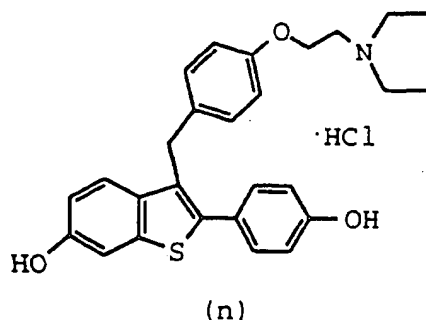


¹H NMR(d₆-DMSO); (2.8ppm, 6H, singlet, N(CH₃)₂); (3.45ppm, 2H, triplet, OCH₂CH₂N); (4.1ppm, 2H, singlet, benzylCH₂); (4.3ppm, 2H, triplet, PhOCH₂CH₂); (6.8ppm, 1H, dd, J=.03, position 5); (6.9ppm, 4H, complex, 3' and 2'); (7.05ppm, 1H, doublet, J=.03, position 4); (7.05ppm, 1H, singlet, position 7); (7.3ppm, 4H, complex, 3" and 2"); (9.6ppm, 1H, singlet, phenol); (9.75ppm, 1H, singlet, phenol); (10.2ppm, 1H, broad peak, HCl). MS(FD) m/z 420 (M⁺-HCl); Anal. Calcd. for: C, 65.85; H, 5.75; N, 3.07. Found: C, 65.64; H, 5.71; N, 3.03.

Example 14

[6-HYDROXY-2-(4-HYDROXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(N,N-DIETHYLAMINO)ETHOXY]PHENYL] METHANE HYDROCHLORIDE

[0089]

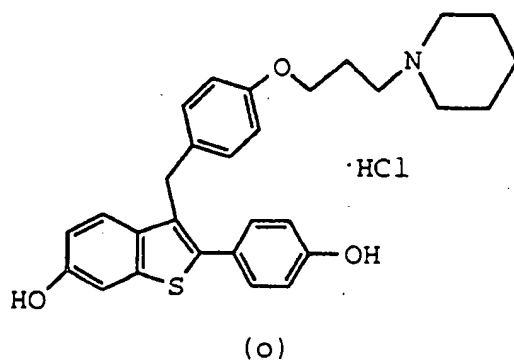


¹H NMR(d₆-DMSO); (1.2ppm, 6H, triplet, NCH₂CH₃); (3.2ppm, 4H, multiplet, NCH₂CH₃); (3.45ppm, 2H, broad peak, PhOCH₂CH₂); (4.1ppm, 2H, singlet, benzylCH₂); (4.3ppm, 2H, triplet, PhOCH₂CH₂); (6.8ppm, 1H, dd, J=.03, position 5); (6.9ppm, 4H, complex, 3' and 2'); (7.05ppm, 1H, doublet, J=.03, position 4); (7.05ppm, 1H, singlet, position 7); (7.3ppm, 4H, complex, 3" and 2"); (9.6ppm, 1H, singlet, phenol); (9.75ppm, 1H, singlet, phenol); (9.95ppm, 1H, broad peak, HCl). MS(FD) m/z 448 (M⁺); Anal. Calcd. for: C, 67.00; H, 6.25; N, 2.89. Found: C, 66.91; H, 6.38; N, 2.80.

Example 15

[6-HYDROXY-2-(4-HYDROXYPHENYL)BENZO[B]THIEN-3-YL][4-[3-(1-PIPERIDINYL)PROPOXY]PHENYL] METHANE HYDROCHLORIDE

[0090]



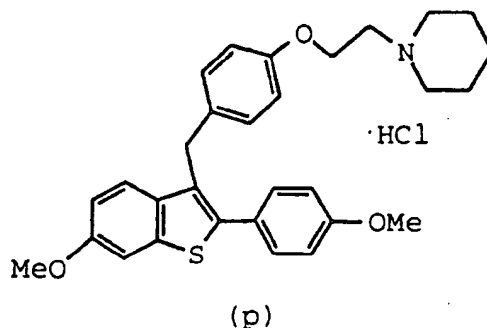
¹H NMR(d₆-DMSO); (1.7ppm, 6H, broad peak, NCH₂CH₂CH₂CH₂); (2.1ppm, 2H, multiplet, PhOCH₂CH₂); (2.85ppm, 2H, broad peak, CH₂NCH₂); (3.15ppm, 2H, multiplet, OCH₂CH₂CH₂N); (3.45ppm, 2H, broad peak, CH₂NCH₂CH₂); (4.0ppm, 2H, triplet, PhOCH₂CH₂); (4.1ppm, 2H, singlet, benzylCH₂); (6.8ppm, 1H, dd, J=.03, position 5); (6.9ppm, 4H, complex, 3' and 2'); (7.05ppm, 1H, doublet, J=.03, position 4); (7.05ppm, 1H, singlet, position 7); (7.3ppm, 4H, complex, 3" and 2"); (9.6ppm, 1H, singlet, phenol); (9.75ppm, 1H, singlet, phenol); (9.95ppm, 1H, broad peak, HCl). MS(FD) m/z 474 (M⁺-HCl); Anal. Calcd. for: C, 68.29; H, 6.32; N, 2.75. Found: C, 62.52; H, 6.59; N, 2.81.

[0091] By following the procedure in Example 9, but using the product of Example 3 as the starting material, Example 16 was prepared.

Example 16

[6-METHOXY-2-(4-METHOXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(1-PIPERIDINYL)ETHOXY]PHENYL] METHANE HYDROCHLORIDE

[0092]

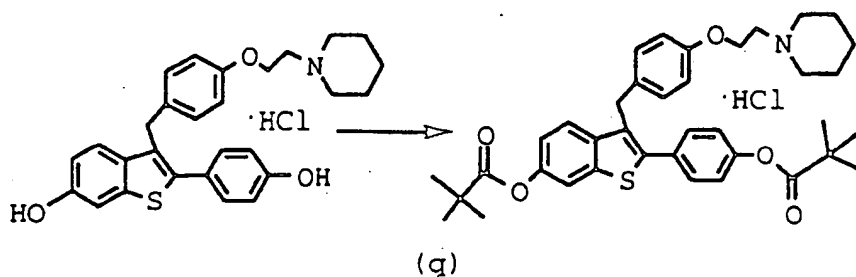


¹H NMR(d₆-DMSO); (1.45ppm, 2H, broad peak, NCH₂CH₂CH₂); (1.85ppm, 4H, broad peak, NCH₂CH₂); (3.05ppm, 2H, broad peak, PhOCH₂CH₂N); (3.5ppm, 4H, broad peak, CH₂NCH₂); (3.9ppm, 6H, singlet, PhOCH₃); (4.25ppm, 2H, singlet, benzylCH₂); (4.4ppm, 2H, triplet, PhOCH₂); (6.95ppm, 1H, doublet, J=.03, position 4); (7.05ppm, 1H, dd, J=.03, position 5); (7.15ppm, 4H, doublet, J=.02, 2' and 3'); (7.5ppm, 4H, doublet, J=.02, 2" and 3"); (7.65ppm, 1H, singlet, position 7); (10.15ppm, 1H, broad peak, HCl). MS(FD) m/z 487 (M+HCl); Anal. Calcd. for: C, 68.74; H, 6.54; N, 2.67. Found: C, 68.50; H, 6.61; N, 2.53.

Example 17

[6-{1,1,1-TRIMETHYLACETOXY}-2-(4-{1,1,1-TRIMETHYLACETOXY}PHENYL)BENZO[B]THIEN-3-YL][4-[2-(1-PIPERIDINYL)ETHOXY]PHENYL] METHANE HYDROCHLORIDE

[0093]



[0094] One gram of the product from Example 11 and 10 mg of dimethylaminopyridine (4-DMAP) were suspended in 100 mL of THF. Triethylamine (2.0 g) was added dropwise over 15 minutes and then dropwise addition of 1.0 g of pivaloyl chloride was conducted over 10 minutes. The reaction mixture was stirred for 16 hours, under nitrogen gas, at ambient temperature. The mixture was then concentrated to dryness and the residue was taken up in 150 mL of dichloromethane and washed 3 times with 100 mL of sodium bicarbonate and once with 150 mL of deionized water. The resulting organic layer was separated, dried on sodium sulfate, and the solvent was removed under vacuum. The resulting thick, colorless oil was then divided into two aliquots in 3 mL of chloroform and each aliquot was run on a chromatatron at 5% methanol in methylene chloride using a 4 mm silica gel plate. The resulting oil was then dissolved in 50 mL of diethyl ether, and a saturated solution of hydrogen chloride gas in diethyl ether, at ambient temperature, was added until no additional precipitate was formed. Excess diethyl ether was decanted off, and the solid phase was

trituated thoroughly in fresh ether. The precipitate was then collected on a vacuum filter to provide 1.1 g of white powder. ^1H NMR(d_6 -DMSO); (1.3ppm, 18H, singlet, $\text{PhOCOC}(\text{CH}_3)_3$); (1.8ppm, 6H, broad peak, $\text{NCH}_2\text{CH}_2\text{CH}_2$); (2.95ppm, 2H, broad peak, $\text{CH}_2\text{NCH}_2\text{CH}_2$); (3.4ppm, 4H, broad peak, $\text{CH}_2\text{CH}_2\text{NCH}_2$); (4.25ppm, 2H, singlet, benzyl CH_2); (4.35ppm, 2H, triplet, $\text{PhOCH}_2\text{CH}_2\text{N}$); (6.9ppm, 2H, doublet, $J=0.03$, 2' position); (7.05ppm, 2H, doublet, $J=0.03$, 3' position); (7.1ppm, 1H, dd, $J=0.02$, position 5); (7.25ppm, 2H, doublet, $J=0.03$, 2" position); (7.55ppm, 2H, doublet, $J=0.03$, 3" position); (7.65ppm, 1H, doublet, $J=0.02$, position 4); (7.8ppm, 1H, singlet, position 7); (10.4ppm, 1H, broad peak, HCl); MS(FD) m/z 700 (M^+-HCl); Anal. Calcd. for: C, 58.72; H, 6.30; N, 1.90. Found: C, 58.57; H, 6.26; N, 1.92.

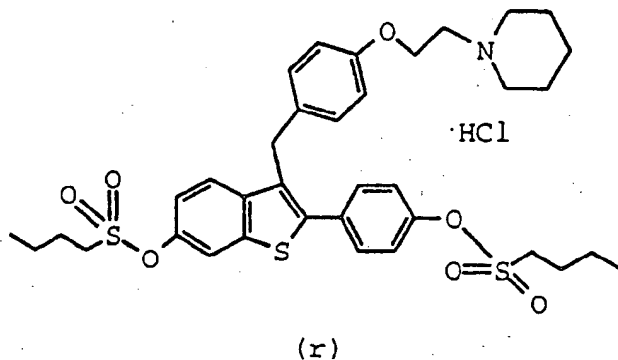
[0095] By following the procedure described in Example 17, and employing the proper reactants, Examples 18, 19, and 20 were prepared.

Example 18

[6-{n-BUTYLSULFONUYLOXY}-2-(4-{n-BUTYLSULFONUYLOXY} PHENYL)BENZO[B]THIEN-3-YL]

[4-[2-(1-PIPERIDINYL)ETHOXY] PHENYL]METHANE HYDROCHLORIDE

[0096]

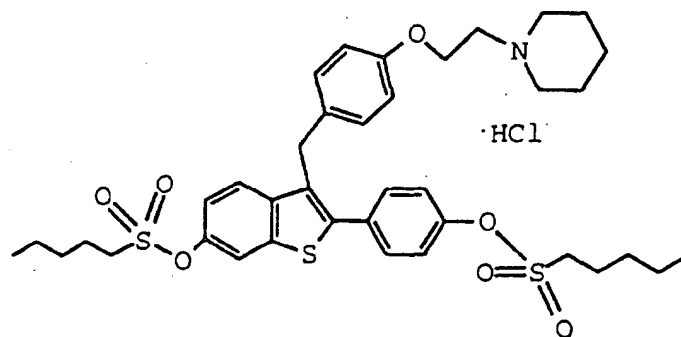


^1H NMR(d_6 -DMSO); (0.9ppm, 6H, triplet, $\text{OSO}_2(\text{CH}_2)_3\text{CH}_3$); (1.45ppm, 6H, multiplet, $\text{OSO}_2(\text{CH}_2)_2\text{CH}_2\text{CH}_3$ and $\text{NCH}_2\text{CH}_2\text{CH}_2$); (1.8ppm, 8H, multiplet, $\text{OSO}_2\text{CH}_2\text{CH}_2$ and NCH_2CH_2); (2.95ppm, 2H, broad peak, CH_2NCH_2); (3.45ppm, 4H, broad peak, $\text{OCH}_2\text{CH}_2\text{NCH}_2$); (3.55ppm, 4H, multiplet, OSO_2CH_2); (4.25ppm, 2H, singlet, benzyl CH_2); (4.3ppm, 2H, triplet, $\text{PhOCH}_2\text{CH}_2$); (6.9ppm, 2H, doublet, $J=0.03$, 2' position); (7.05ppm, 2H, doublet, $J=0.03$, 3' position); (7.3ppm, 1H, dd, $J=0.03$, position 5); (7.5ppm, 2H, doublet, $J=0.02$, 2" position); (7.65ppm, 2H, doublet, $J=0.02$, 3" position); (7.7ppm, 1H, doublet, $J=0.03$, position 4); (8.1ppm, 1H, singlet, 7 position); (10.1ppm, 1H, broad peak, HCl). MS(FD) m/z 668 (M^+-HCl); Anal. Calcd. for C, 75.54; H, 5.58; N, 2.10. Found: C, 75.33; H, 5.61; N, 2.20.

Example 19

**[6-(n-PENTYLSULFONOYL)-2-(4-(n-PENTYLSULFONOYL)PHENYL) BENZO[B]THIEN-3-YL]
[4-[2-(1-PIPERIDENYL)ETHOXY] PHENYL]METHANE HYDROCHLORIDE**

[0097]

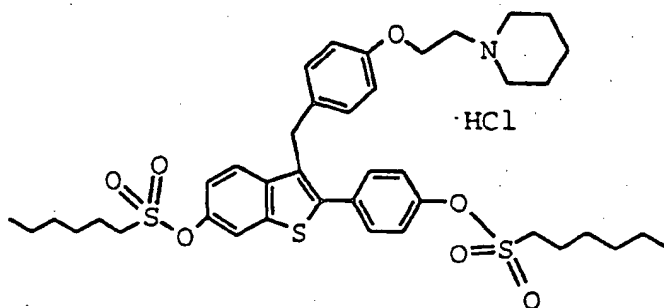


Anal. Calcd. for C, 59.71; H, 6.59; N, 1.83. Found: C, 59.51; H, 6.43; N, 1.73.

Example 20

**6-(n-HEXYLSULFONOYL)-2-(4-n-HEXYLSULFONOYL)PHENYL)BENZO [B]THIEN-3-YL)[4-[2-(1-PIPERIDENYL)
ETHOXY]PHENYL]METHANE HYDROCHLORIDE**

[0098]



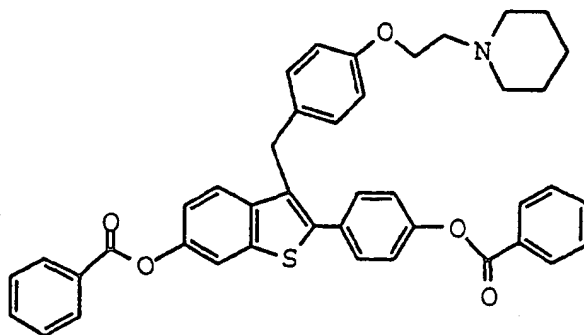
Anal. Calcd. for C, 60.62; H, 6.87; N, 1.77. Found: C, 60.13; H, 7.08; N, 1.68.

[0099] By following the procedures in Example 17 and employing the proper reactants, but not preparing the hydrochloride salt, Example 21 was prepared.

Example 21

[6-BENZOYLOXY-2-(4-BENZOYLOXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(1-PIPERIDINYL)ETHOXY]PHENYL]METHANE

[0100]



(s)

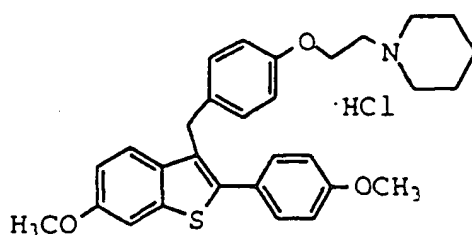
¹H NMR(d₆-DMSO); (1.35ppm, 2H, broad peak, NCH₂CH₂CH₂); (1.5ppm, 4H, broad peak, NCH₂CH₂); (2.4ppm, 4H, broad peak, OCH₂CH₂NCH₂); (2.65ppm, 2H, broad peak, OCH₂CH₂N); (4.0ppm, 2H, triplet, PhOCH₂CH₂); (4.25ppm, 2H, singlet, benzylCH₂); (6.85ppm, 2H, doublet, J=.03, 2' position); (7.05ppm, 2H, doublet, J=.03, 3' position); (7.3ppm, 1H, dd, J=.02, position 5); (7.45ppm, 2H, doublet, J=.03, 2'' position); (7.70ppm, 9H, complex, benzoateH, 3'' position, and position 4); (8.05ppm, 1H, singlet, position 7); (8.2ppm, 4H, doublet, J=.03, OCOCCH₃). MS FD+ = 628; Anal. Calcd. for: C, 75.54; H, 5.58; N, 2.10.

Found: C, 75.33; H, 5.61; N, 2.20.

Example 22

[6-METHOXY-2-(4-METHOXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(1-PIPERIDINYL)ETHOXY]PHENYL]METHANE HYDROCHLORIDE

[0101]



(t)

[0102] To 20 mL of n-propylbenzene was added 500 mg (12.52 mmol) of 95% lithium aluminum hydride and 500 mg (0.929 mmol) of [6-methoxy-2-(4-methoxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone. The mixture was heated to reflux for 40 minutes and then allowed to cool to ambient temperature. To the mixture was carefully added 1 mL of deionized water followed by 3 mL of 15% aqueous sodium hydroxide and then an additional 1 mL of deionized water. The mixture was stirred for 15 minutes at ambient temperature and the precipitate then was removed by vacuum filter. The resulting mother liquor was diluted with 100 mL of methylene chloride, washed once with brine, dried on sodium sulfate, and concentrated to dryness. The resulting clear gum was purified by radial chromatography on a 4 mm plate using a 19:1 ratio of methylene chloride:methanol as eluent. The clear gum was taken

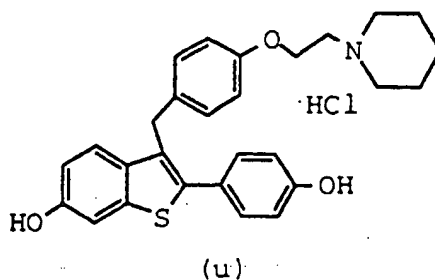
up in a minimal amount of methanol and then a saturated solution of methanol/HCl (g) was added. The product was crystallized from acetone to yield 350 mg of the desired product as an off-white amorphous material (49%): NMR QE300 MHz in d₆-DMSO: (1.30-1.40ppm, m, 1H), (1.60-1.80ppm, complex, 5H), (2.90-3.00ppm, m, 2H), (3.40ppm-3.50ppm, complex, 4H), (3.79ppm, s, 3H), 3.81ppm, s, 3H), (4.15ppm, s, 2H), (4.35ppm t, 2H), (6.85ppm, d, 2H), (6.95ppm, dd, 1H), (7.05ppm, d, 4H), (7.45ppm, d, 4H), (7.55ppm, ds, 1H). FD+ MS = 487. Anal. Calcd. for: C, 68.75; H, 6.54; N, 2.67.

Found: C, 67.60; H, 6.58; N, 2.44.

Example 23

[6-HYDROXY-2-(4-HYDROXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(1-PIPERIDINYL)ETHOXY]PHENYL] METHANE HYDROCHLORIDE

[0103]

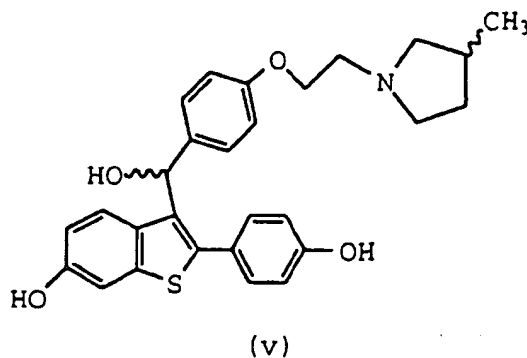


[0104] To a suspension of [6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl] methanone (as described in U.S. Pat. No. 4,418,068) (0.51 g, 1.00 mmol) stirring in n-propylbenzene was added Red-Ak® (0.87 g, 6.00 mmol), and the mixture was heating to reflux. After 3 hours, the solution was cooled to ambient temperature and carefully quenched with excess 1.0 N HCl. The resulting biphasic mixture was extracted with ethyl acetate and the combined organic extracts washed with saturated aqueous bicarbonate, brine, dried (magnesium sulfate), filtered, and concentrated. Purification of the crude material by radial chromatography (silica gel, ethyl acetate/hexanes/methanol-triethylamine (2.5/2.5/0.7/0.3) gave the title compound as a tan solid: ¹H-NMR (300 MHz, acetone-d₆) δ 7.28-7.37 (complex, 3H), 7.08 (d, J = 8.9 Hz, 2H), 6.75-6.90 (complex, 6H), 4.15 (s, 2H), 4.01 (t, J = 3.8 Hz, 2H), 2.68 (s, J = 4.0 Hz, 2H), 2.45 (m, 4H), 1.494-1.56 (complex, 4H), 1.33-1.41 (complex, 2H).

Example 24

[6-HYDROXY-2-(4-HYDROXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(3-METHYL-1-PIPERIDINYL)ETHOXY]PHENYL]METHANOL

[0105]

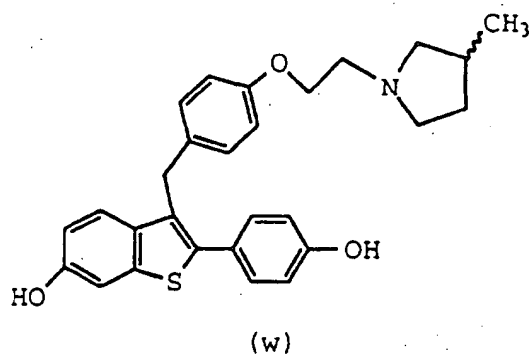


[0106] A solution of [6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thien-3-yl][4-[2-(3-methyl-1-piperidinyloxy)phenyl]methanone, as described in United Kingdom Patent Application GB 2097 788 H (0.300 g, 0.633 mmol), was stirred in THF (40 mL) at ambient temperature. Lithium aluminum hydride (0.100 g, 2.64 mmol) was added gradually over a 15 minute period and the reaction mixture was stirred at ambient temperature for 1.75 hours. Subsequently, the reaction was quenched with cold ethyl acetate. The mixture was evaporated and then taken up in methanol (10 mL) and ethyl acetate (30 mL). The organic layers were washed with sodium bicarbonate (25 mL of a saturated aqueous solution), potassium sodium tartrate (3 x 20 mL, saturated aqueous solution), and dried (magnesium sulfate). Concentration gave 0.290 g (96%) of the title compound which was used without further purification: ¹H NMR (300 MHz, MeOD-d₄) δ 7.50 (d, 1H, J = 8 Hz), 7.34 (d, 2H, J = 8 Hz), 7.28 (d, 2H, J = 8 Hz), 7.16 (d, 1H, J = 2 Hz), 6.83-6.90 (m, 4H), 6.68 (dd, 1H, J = 8 Hz, J = 2 Hz), 6.10 (s, 1H), 4.13 (t, 2H, J = 6 Hz), 3.00-3.25 (m, 4H), 2.85-2.92 (m, 1H), 2.32-2.43 (m, 2H), 2.08-2.19 (m, 1H), 1.42-1.51 (m, 1H), 1.05 (d, 2H, J = 6 Hz); IR (KBr) 3251, 2958, 1610, 1509, 1238 1171, 838 cm⁻¹; MS (FD) m/z 476 (M⁺).

Example 25

[6-HYDROXY-2-(4-HYDROXYPHENYL)BENZO[B]THIEN-3-YL][4-[2-(3-METHYL-1-PIPERIDINYL)ETHOXY]PHENYL]METHANE

[0107]

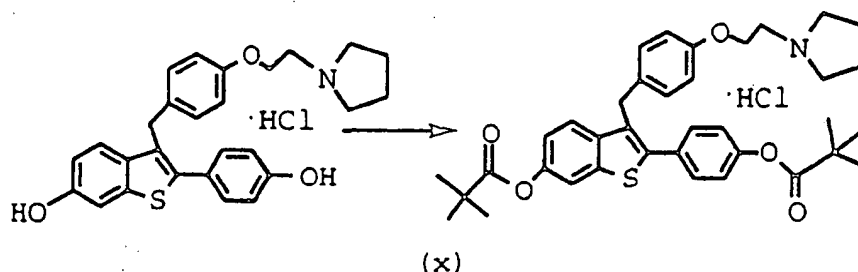


[0108] To a suspension of the product of Example 24 (0.466 g, 0.980 mmol) stirring in dichloromethane (24 mL) at 0° C was added triethylsilane (0.94 mL, 5.8 mmol). After 10 minutes, trifluoroacetic acid (6.4 mL) was added at such a rate that the temperature was maintained below 5° C. The resulting solution was stirred at 0° C for 2 hours, then quenched by pouring it into a saturated aqueous sodium bicarbonate solution (50 mL). Methanol was added as necessary to dissolve any residue. This mixture was then extracted with ethyl acetate (2 x 200 mL). The combined extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by radial chromatography (4 mm, silica gel, 8:2 ethyl acetate/methanol) gave 0.304 g (68%) of the title compound as a white foam: ¹H NMR (300 MHz, MeOD-d₄) δ 7.26-7.30 (m, 3H), 7.18 (d, 1H, J = 2.2 Hz), 7.03 (d, 2H, J = 8.6 Hz), 6.74-6.83 (m, 5H), 4.07-4.11 (m, 4H), 3.00-3.20 (m, 4H), 2.80-2.85 (m, 1H), 2.35-2.41 (m, 2H), 2.05-2.18 (m, 1H), 1.43-1.48 (m, 1H), 1.06 (t, 3H, J = 6.2 Hz); IR (KBr) 3385, 2958, 1677, 1610, 1509, 1239, 837 cm⁻¹; MS (FD) m/z 460 (m⁺).

Example 26

**[6-{1,1,1-TRIMETHYLACETOXY}-2-(4-{1,1,1-TRIMETHYLACETOXY}PHENYL)BENZO[B]THIEN-3-YL]
[4-{2-(3-METHYL-1-PIPERIDINYL)ETHOXY}PHENYL] METHANE HYDROCHLORIDE**

[0109]



[0110] To a solution of the product of Example 25, (0.250 g, 0.544 mmol) stirring at ambient temperature in THF (25 mL) was added N,N-dimethylaminopyridine (2 mg) followed by triethylamine (0.7 mL, 5 mmol). After 10 minutes, pivaloyl chloride (0.27 mL, 2.18 mmol) was added dropwise and the reaction stirred at ambient temperature. After 16 hours, the solution was quenched by pouring into ethyl acetate (50 mL) and water (50 mL). The organic layer was separated, and the aqueous sodium bicarbonate (2 x 25 mL), brine (25 mL), dried over anhydrous magnesium sulfate, and concentrated. Purification by radial chromatography (2 mm, silica gel, 8:2 ethyl acetate/methanol) gave 0.291 g (85%) of the desired compound as a thick oil: ¹H NMR (300 MHz, CDCl₃) δ 7.55 (d, 1H, J = 2.1 Hz), 7.46-7.50 (m, 3H), 7.09 (d, 2H, J = 8.9 Hz), 6.96-7.02 (m, 3H), 6.80 (d, 2H, J = 8.5 Hz), 4.18 (s, 2H), 4.04 (t, 2H, J = 6 Hz), 2.81-3.00 (m, 4H), 2.50-2.59 (m, 1H), 2.22-2.35 (m, 1H), 2.02-2.18 (m, 2H), 1.59-1.64 (m, 1H), 1.37 (s, 9H), 1.36 (s, 9H), 1.02 (d, 3H, J = 6.7 Hz); IR (CHCl₃) 2985, 1751, 1516, 1134 cm⁻¹; MS (FD) m/z 628 (M⁺).

[0111] The compounds of formula I of the present invention are useful for alleviating the symptoms of post-menopausal syndrome, particularly osteoporosis, associated cardiovascular diseases, particularly hyperlipidemia, and estrogen-dependent cancer, particularly estrogen-dependent breast and uterine carcinoma. The term "alleviating" is defined to include prophylactically treating a woman from incurring one or more symptoms/ pathological conditions of post-menopausal syndrome, holding in check such symptoms/pathological conditions, and/or treating existing symptoms/pathological conditions. As such, the present methods include both medical therapeutic and/or prophylactic treatment, as appropriate.

[0112] Compounds of formula I, also are effective for inhibiting uterine fibroid disease and endometriosis in women, and smooth muscle cell proliferation in humans. The following non-limiting test examples illustrate the methods of the present invention.

Test Procedure**General Preparation Procedure**

[0113] In the examples illustrating the methods, a post-menopausal model was used in which effects of different treatments upon circulating lipids were determined.

[0114] Seventy-five day old female Sprague Dawley rats (weight range of 200 to 225g) were obtained from Charles River Laboratories (Portage, MI). The animals were either bilaterally ovariectomized (OVX) or exposed to a Sham surgical procedure at Charles River Laboratories, and then shipped after one week. Upon arrival, they were housed in metal hanging cages in groups of 3 or 4 per cage and had *ad libitum* access to food (calcium content approximately 0.5%) and water for one week. Room temperature was maintained at 22.2° ± 1.7° C with a minimum relative humidity of 40%. The photoperiod in the room was 12 hours light and 12 hours dark.

[0115] **Dosing Regimen Tissue Collection.** After a one week acclimation period (therefore, two weeks post-OVX) daily dosing with test compound was initiated. 17α-ethynyl estradiol or the test compound were given orally, unless otherwise stated, as a suspension in 1% carboxymethylcellulose or dissolved in 20% cyclodextrin. Animals were dosed daily for 4 days. Following the dosing regimen, animals were weighed and anesthetized with a ketamine: Xylazine (2:1, V:V) mixture and a blood sample was collected by cardiac puncture. The animals were then sacrificed by asphyxiation with CO₂, the uterus was removed through a midline incision, and a wet uterine weight was determined.

[0116] Cholesterol Analysis. Blood samples were allowed to clot at room temperature for 2 hours, and serum was obtained following centrifugation for 10 minutes at 3000 rpm. Serum cholesterol was determined using a Boehringer Mannheim Diagnostics high performance cholesterol assay. Briefly the cholesterol was oxidized to cholest-4-en-3-one and hydrogen peroxide. The hydrogen peroxide was then reacted with phenol and 4-aminophenazone in the presence of peroxidase to produce a p-quinone imine dye, which was read spectrophotometrically at 500 nm. Cholesterol concentration was then calculated against a standard curve. The entire assay was automated using a Biomek Automated Workstation.

[0117] Uterine Eosinophil Peroxidase (EPO) Assay. Uteri were kept at 4° C until time of enzymatic analysis. The uteri were then homogenized in 50 volumes of 50 mM Tris buffer (pH - 8.0) containing 0.005% Triton X-100. Upon addition of 0.01% hydrogen peroxide and 10 mM o-phenylenediamine (final concentrations) in Tris buffer, increase in absorbance was monitored for one minute at 450 nm. The presence of eosinophils in the uterus is an indication of estrogenic activity of a compound. The maximal velocity of a 15 second interval was determined over the initial, linear portion of the reaction curve.

[0118] Source of Compound: 17 α -ethynyl estradiol was obtained from Sigma Chemical Co., St. Louis, MO.

Influence of Formula I Compounds on Serum Cholesterol and Determination of Agonist/Non-Agonist Activity

[0119] Data presented in Tables 1-4 below show comparative results among ovariectomized rats, rats treated with 17 α -ethynyl estradiol (EE₂; an orally available form of estrogen), and rats treated with certain compounds of the present invention. Although EE₂ caused a decrease in serum cholesterol when orally administered at 0.1 mg/Kg/day, it also exerted a stimulatory action on the uterus so that EE₂ uterine weight was substantially greater than the uterine weight of ovariectomized test animals. This uterine response to estrogen is well recognized in the art.

[0120] Not only did the compounds of the present invention substantially reduce serum cholesterol compared to the ovariectomized control animals, but uterine weight was only minimally increased to slightly decreased. Compared to estrogenic compounds known in the art, the benefit of serum cholesterol reduction without adversely affecting uterine weight is quite rare and desirable.

[0121] As is expressed in the below data, estrogenicity also was assessed by evaluating the adverse response of eosinophil infiltration into the uterus. The compounds of the present invention did not cause any increase in the number of eosinophils observed in the stromal layer of ovariectomized rats, while estradiol cause a substantial, expected increase in eosinophil infiltration.

[0122] The data presented in the following Tables 1-4 reflect the response of 5 to 6 rats per treatment.

Table 1

Compound	Dose mg/kg	Uterine Weight (% increase vs. OVX)	Uterine EPO (V. max)	Serum Cholesterol (% decrease vs. OVX)
EE ₂	0.1	111.5	246.0	89.5
(k)-Ex11*	0.1	4.0	7.3	43.7
	1.0	23.1	4.8	63.0
	10.0	5.2	5.5	60.7

*refers to the letter designation given to a compound described in the stated Example, infra.

Table 2

Compound	Dose mg/kg	Uterine Weight (% increase vs. OVX)	Uterine EPO (V. max)	Serum Cholesterol (% decrease vs. OVX)
EE ₂	0.1	178.3	173.3	91.8
(b)-Ex2*	0.1	52.2	7.4	22.2
	1.0	39.1	4.7	43.5
	10.0	45.6	14.5	61.6

*refers to the letter designation given to a compound described in the stated Example, infra.

Table 3

Compound	Dose mg/kg	Uterine Weight (% increase vs. OVX)	Uterine EPO (V. max)	Serum Cholesterol (% decrease vs. OVX)
EE ₂	0.1	181.5	133.1	86.4
(k) -EX11*	0.1	32.7	7.6	56.0
	1.0	-5.0	2.2	58.2
	10.0	-0.8	4.2	56.5

*refers to the letter designation given to a compound described in the stated Example, infra.

Table 4

Compound	Dose mg/kg	Uterine Weight (% increase vs. OVX)	Uterine EPO (V. max)	Serum Cholesterol (% decrease vs. OVX)
EE ₂	0.1	178.3	173.3	91.8
(p)-Ex16*	0.1	-13.5	5.8	26.8
	1.0	-13.7	5.4	59.4
	10.0	-24.6	6.2	72.3
(q)-Ex17	0.1	-22.7	3.1	55.8
	1.0	-32.4	3.0	56.8
	10.0	-25.2	2.8	58.8
(r)-Ex18	0.1	-16.6	1.8	65.4
	1.0	-18.4	3.5	67.0
	10.0	-19.5	2.8	67.9
(s)-Ex21	0.1	-19.6	1.8	66.2
	1.0	-28.7	2.6	63.4
	10.0	-26.6	2.3	64.4

*refers to the letter designation given to a compound described in the stated Example, infra.

[0123] In addition to the demonstrated benefits of the compounds of the present invention, especially when compared to estradiol, the above data clearly demonstrate that compounds of Formula I are not estrogen mimetics. Furthermore, no deleterious toxicological effects (survival) were observed with any treatment.

Osteoporosis Test Procedure

[0124] Following the General Preparation Procedure, infra, the rats were treated daily for 35 days (6 rats per treatment group) and sacrificed by decapitation on the 36th day. The 35 day time period was sufficient to allow maximal reduction in bone density, measured as described herein. At the time of sacrifice, the uteri were removed, dissected free of extraneous tissue, and the fluid contents were expelled before determination of wet weight in order to confirm estrogen deficiency associated with complete ovariectomy. Uterine weight was routinely reduced about 75% in response to ovariectomy. The uteri were then placed in 10% neutral buffered formalin to allow for subsequent histological analysis.

[0125] The right femurs were excised and scanned at the distal metaphysis 1 mm from the patellar groove with single photon absorptiometry. Results of the densitometer measurements represent a calculation of bone density as a function of the bone mineral content and bone width.

[0126] In accordance with the above procedures, compounds of the present invention and ethynyl estradiol (EE₂) in 20% hydroxypropyl β -cyclodextrin were orally administered to test animals. Data presented in Tables 5 and 6 below are the results of these treatments compared to intact and ovariectomized test animals. Results are reported as the mean \pm the standard error of the mean.

Table 5

Compound/ Treatment	Dose /kg	Bone Density mg/cm/cm
Ovariectomy control (20% cyclodextrin)	-	26.18 ± 5.52
Intact control (20% cyclodextrin)	-	70.22* ± 9.82
EE ₂	100 µg/kg	47.94 ± 3.71
(p)-Ex16 ¹	0.01 mg/kg	26.78 ± 4.98
	0.1 mg/kg	43.30 ± 7.86
	1.0 mg/kg	33.62 ± 5.87
	10.0 mg/kg	55.65* ± 6.77
(q)-Ex17	0.01 mg/kg	17.63 ± 2.94
	0.1 mg/kg	24.77 ± 4.65
	1.0 mg/kg	54.09* ± 8.16
	10.0 mg/kg	46.24* ± 4.35

*: P ≤ 0.05, two tailed Student's T test on raw data.

1 - refers to the letter designation given to a compound described in the stated Example, infra.

Table 6

Compound/ Treatment	Dose	Bone Density mg/cm/cm
Ovariectomy control (20% cyclodextrin)	-	32.46 ± 5.76
Intact control (20% cyclodextrin)	-	81.27* ± 8.09
EE ₂	100 µg/kg	47.31 ± 6.42
(q)-Ex17 ¹	0.01 mg/kg	36.44 ± 4.4
	0.1 mg/kg	54.25* ± 8.66
	1.0 mg/kg	36.07 ± 4.20
	10.0 mg/kg	60.34* ± 6.44

*: P ≤ 0.05, two tailed Student's T test on raw data.

1 - refers to the letter designation given to a compound described in the stated Example, infra.

[0127] In summary, ovariectomy of the test animals caused a significant reduction in femur density compared to intact, vehicle treated controls. Orally administered ethynyl estradiol (EE₂) prevented this loss, but the risk of uterine stimulation with this treatment is ever-present.

[0128] The compounds of the present invention also prevented bone loss in a general, dose-dependent manner. Accordingly, the compounds of the present invention are useful for the treatment of post-menopausal syndrome, particularly osteoporosis.

MCF-7 Proliferation Assay

[0129] MCF-7 breast adenocarcinoma cells (ATCC HTB 22) were maintained in MEM (minimal essential medium, phenol red-free, Sigma, St. Louis, MO) supplemented with 10% fetal bovine serum (FBS) (V/V), L-glutamine (2 mM), sodium pyruvate (1 mM), HEPES {(N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]) 10 mM}, non-essential amino acids and bovine insulin (1 µg/mL) (maintenance medium). Ten days prior to assay, MCF-7 cells were switched to maintenance medium supplemented with 10% dextrancoated charcoal stripped fetal bovine serum (DCC-FBS) assay medium) in place of 10% FBS to deplete internal stores of steroids. MCF-7 cells were removed from maintenance flasks using cell dissociation medium (Ca⁺⁺/Mg⁺⁺ free HBSS (phenol red-free) supplemented with 10 mM HEPES and 2 mM EDTA). Cells were washed twice with assay medium and adjusted to 80,000 cells/mL. Approximately 100 µL (8,000 cells) were added to flat-bottom microculture wells (Costar 3596) and incubated at 37° C in a 5% CO₂ humidified incubator for 48 hours to allow for cell adherence and equilibration after transfer. Serial dilutions of drugs or DMSO as a diluent control were prepared in assay medium and 50 µL transferred to triplicate microcultures followed by 50 µL assay medium for a final volume of 200 µL. After an additional 48 hours at 37° C in a 5% CO₂ humidified incubator, microcultures were pulsed with tritiated thymidine (1 µCi/well) for 4 hours. Cultures were terminated by freezing at -70° C for 24 hours followed by thawing and harvesting of microcultures using a Skatron Semiautomatic Cell Harvester. Samples were counted by liquid scintillation using a Wallac BetaPlace β counter. Results in Table 7

below show the IC₅₀ for certain compounds of the present invention.

Table 7

Compound/Treatment	IC ₅₀ nM
Estrone	1
(p) -Ex16*	50
(q)-Ex17	0.01
(r)-Ex18	1000
(s)-Ex21	0.01

*refers to the letter designation given to a compound described in the stated Example, infra.

DMBA-Induced Mammary Tumor Inhibition

[0130] Estrogen-dependent mammary tumors are produced in female Sprague-Dawley rats which are purchased from Harlan Industries, Indianapolis, Indiana. At about 55 days of age, the rats receive a single oral feeding of 20 mg of 7,12-dimethylbenz[a]anthracene (DMBA). About 6 weeks after DMBA administration, the mammary glands are palpated at weekly intervals for the appearance of tumors. Whenever one or more tumors appear, the longest and shortest diameters of each tumor are measured with a metric caliper, the measurements are recorded, and that animal is selected for experimentation. An attempt is made to uniformly distribute the various sizes of tumors in the treated and control groups such that average-sized tumors are equivalently distributed between test groups. Control groups and test groups for each experiment contain 5 to 9 animals.

[0131] Compounds of Formula I are administered either through intraperitoneal injections in 2% acacia, or orally. Orally administered compounds are either dissolved or suspended in 0.2 mL corn oil. Each treatment, including acacia and corn oil control treatments, is administered once daily to each test animal. Following the initial tumor measurement and selection of test animals, tumors are measured each week by the above-mentioned method. The treatment and measurements of animals continue for 3 to 5 weeks at which time the final areas of the tumors are determined. For each compound and control treatment, the change in the mean tumor area is determined.

Uterine Fibrosis Test Procedures

Test 1

[0132] Between 3 and 20 women having uterine fibrosis are administered a compound of the present invention. The amount of compound administered is from 0.1 to 1000 mg/day, and the period of administration is 3 months.

[0133] The women are observed during the period of administration, and up to 3 months after discontinuance of administration, for effects on uterine fibrosis.

Test 2

[0134] The same procedure is used as in Test 1, except the period of administration is 6 months.

Test 3

[0135] The same procedure is used as in Test 1, except the period of administration is 1 year.

Test 4

A. Induction of fibroid tumors in guinea pig.

[0136] Prolonged estrogen stimulation is used to induce leiomyomata in sexually mature female guinea pigs. Animals are dosed with estradiol 3-5 times per week by injection for 2-4 months or until tumors arise. Treatments consisting of a compound of the invention or vehicle is administered daily for 3-16 weeks and then animals are sacrificed and the uteri harvested and analyzed for tumor regression.

B. Implantation of human uterine fibroid tissue in nude mice.

[0137] Tissue from human leiomyomas are implanted into the peritoneal cavity and or uterine myometrium of sexually mature, castrated, female, nude mice. Exogenous estrogen are supplied to induce growth of the explanted tissue. In some cases, the harvested tumor cells are cultured *in vitro* prior to implantation. Treatment consisting of a compound of the present invention or vehicle is supplied by gastric lavage on a daily basis for 3-16 weeks and implants are removed and measured for growth or regression. At the time of sacrifice, the uteri is harvested to assess the status of the organ.

Test 5

[0138] A. Tissue from human uterine fibroid tumors is harvested and maintained, *in vitro*, as primary nontransformed cultures. Surgical specimens are pushed through a sterile mesh or sieve, or alternately teased apart from surrounding tissue to produce a single cell suspension. Cells are maintained in media containing 10% serum and antibiotic. Rates of growth in the presence and absence of estrogen are determined. Cells are assayed for their ability to produce complement component C3 and their response to growth factors and growth hormone. *In vitro* cultures are assessed for their proliferative response following treatment with progestins, GnRH, a compound of the present invention and vehicle. Levels of steroid hormone receptors are assessed weekly to determine whether important cell characteristics are maintained *in vitro*. Tissue from 5-25 patients are utilized.

[0139] Activity in at least one of the above tests indicates the compounds of the present invention are of potential in the treatment of uterine fibrosis.

Endometriosis Test Procedure

[0140] In Tests 1 and 2, effects of 14-day and 21-day administration of compounds of the present invention on the growth of explanted endometrial tissue can be examined.

Test 1

[0141] Twelve to thirty adult CD strain female rats are used as test animals. They are divided into three groups of equal numbers. The estrous cycle of all animals is monitored. On the day of proestrus, surgery is performed on each female. Females in each group have the left uterine horn removed, sectioned into small squares, and the squares are loosely sutured at various sites adjacent to the mesenteric blood flow. In addition, females in Group 2 have the ovaries removed.

[0142] On the day following surgery, animals in Groups 1 and 2 receive intraperitoneal injections of water for 14 days whereas animals in Group 3 receive intraperitoneal injections of 1.0 mg of a compound of the present invention per kilogram of body weight for the same duration. Following 14 days of treatment, each female is sacrificed and the endometrial explants, adrenals, remaining uterus, and ovaries, where applicable, are removed and prepared for histological examination. The ovaries and adrenals are weighed.

Test 2

[0143] Twelve to thirty adult CD strain female rats are used as test animals. They are divided into two equal groups. The estrous cycle of all animals is monitored. On the day of proestrus, surgery is performed on each female. Females in each group have the left uterine horn removed, sectioned into small squares, and the squares are loosely sutured at various sites adjacent to the mesenteric blood flow.

[0144] Approximately 50 days following surgery, animals assigned to Group 1 receive intraperitoneal injections of water for 21 days whereas animals in Group 2 receive intraperitoneal injections of 1.0 mg of a compound of the present invention per kilogram of body weight for the same duration. Following 21 days of treatment, each female is sacrificed and the endometrial explants and adrenals are removed and weighed. The explants are measured as an indication of growth. Estrous cycles are monitored.

Test 3

A. Surgical induction of endometriosis

[0145] Autographs of endometrial tissue are used to induce endometriosis in rats and/or rabbits. Female animals at reproductive maturity undergo bilateral oophorectomy, and estrogen is supplied exogenously thus providing a specific

and constant level of hormone. Autologous endometrial tissue is implanted in the peritoneum of 5-150 animals and estrogen supplied to induce growth of the explanted tissue. Treatment consisting of a compound of the present invention is supplied by gastric lavage on a daily basis for 3-16 weeks, and implants are removed and measured for growth or regression. At the time of sacrifice, the intact horn of the uterus is harvested to assess status of endometrium.

B. Implantation of human endometrial tissue in nude mice.

[0146] Tissue from human endometrial lesions is implanted into the peritoneum of sexually mature, castrated, female, nude mice. Exogenous estrogen is supplied to induce growth of the explanted tissue. In some cases, the harvested endometrial cells are cultured *in vitro* prior to implantation. Treatment consisting of a compound of the present invention supplied by gastric lavage on a daily basis for 3-16 weeks, and implants are removed and measured for growth or regression. At the time of sacrifice, the uteri are harvested to assess the status of the intact endometrium.

Test 4

[0147] A. Tissue from human endometrial lesions is harvested and maintained *in vitro* as primary nontransformed cultures. Surgical specimens are pushed through a sterile mesh or sieve, or alternately teased apart from surrounding tissue to produce a single cell suspension. Cells are maintained in media containing 10% serum and antibiotic. Rates of growth in the presence and absence of estrogen are determined. Cells are assayed for their ability to produce complement component C3 and their response to growth factors and growth hormone. *In vitro* cultures are assessed for their proliferative response following treatment with progestins, GnRH, a compound of the invention, and vehicle. Levels of steroid hormone receptors are assessed weekly to determine whether important cell characteristics are maintained *in vitro*. Tissue from 5-25 patients is utilized.

[0148] Activity in any of the above assays indicates that the compounds of the present invention are useful in the treatment of endometriosis.

Inhibition of Aortal Smooth Cell Proliferation/Restenosis Test Procedure

[0149] Compounds of the present invention have capacity to inhibit aortal smooth cell proliferation. This can be demonstrated by using cultured smooth cells derived from rabbit aorta, proliferation being determined by the measurement of DNA synthesis. Cells are obtained by explant method as described in Ross, *J. of Cell Bio.* 50: 172 (1971). Cells are plated in 96 well microtiter plates for five days. The cultures become confluent and growth arrested. The cells are then transferred to Dulbecco's Modified Eagle's Medium (DMEM) containing 0.5 - 2% platelet poor plasma, 2 mM L-glutamine, 100 U/ml penicillin, 100 mg/ml streptomycin, 1 mCi/ml ³H-thymidine, 20 ng/ml platelet-derived growth factor, and varying concentrations of the present compounds. Stock solution of the compounds is prepared in dimethyl sulphoxide and then diluted to appropriate concentration (0.01 - 30 mM) in the above assay medium. Cells are then incubated at 37° C. for 24 hours under 5% CO₂/95% air. At the end of 24 hours, the cells are fixed in methanol. ³H thymidine incorporation in DNA is then determined by scintillation counting as described in Bonin, *et al.*, *Exp. Cell Res.* 181: 475-482 (1989).

[0150] Inhibition of aortal smooth muscle cell proliferation by the compounds of the present invention are further demonstrated by determining their effects on exponentially growing cells. Smooth muscle cells from rabbit aortae are seeded in 12 well tissue culture plates in DMEM containing 10% fetal bovine serum, 2 mM L-glutamine, 100 U/ml penicillin, and 100 mg/ml streptomycin. After 24 hours, the cells are attached and the medium is replaced with DMEM containing 10% serum, 2 mM L-glutamine, 100 U/ml penicillin, 100 mg/ml streptomycin, and desired concentrations of the compounds. Cells are allowed to grow for four days. Cells are treated with trypsin and the number of cells in each culture is determined by counting using a ZM-Coulter counter.

[0151] Activity in the above tests indicates that the compounds of the present invention are of potential in the treatment of restenosis.

[0152] The present invention also provides a method of alleviating post-menopausal syndrome in women which comprises the aforementioned method using compounds of Formula I and further comprises administering to a woman an effective amount of estrogen or progestin. These treatments are particularly useful for treating osteoporosis and lowering serum cholesterol because the patient will receive the benefits of each pharmaceutical agent while the compounds of the present invention would inhibit undesirable side-effects of estrogen and progestin. Activity of these combination treatments in any of the post-menopausal tests, *infra*, indicates that the combination treatments are useful for alleviating the symptoms of post-menopausal symptoms in women.

[0153] Various forms of estrogen and progestin are commercially available. Estrogen-based agents include, for example, ethenyl estrogen (0.01 - 0.03 mg/day), mestranol (0.05 - 0.15 mg/day), and conjugated estrogenic hormones such as Premarin® (Wyeth-Ayerst; 0.3 - 2.5 mg/day). Progestin-based agents include, for example, medroxyproges-

terone such as Provera® (Upjohn; 2.5 -10 mg/day), norethynodrel (1.0 - 10.0 mg/day), and norethindrone (0.5 - 2.0 mg/day). A preferred estrogen-based compound is Premarin, and norethynodrel and norethindrone are preferred progestin-based agents.

[0154] The method of administration of each estrogen- and progestin-based agent is consistent with that which is known in the art. For the majority of the methods of the present invention, compounds of Formula I are administered continuously, from 1 to 3 times daily. However, cyclical therapy may especially be useful in the treatment of endometriosis or may be used acutely during painful attacks of the disease. In the case of restenosis, therapy may be limited to short (1-6 months) intervals following medical procedures such as angioplasty.

[0155] As used herein, the term "effective amount" means an amount of compound of the present invention which is capable of alleviating the symptoms of the various pathological conditions herein described. The specific dose of a compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case including, for example, the compound administered, the route of administration, the state of being of the patient, and the pathological condition being treated. A typical daily dose will contain a nontoxic dosage level of from about 5 mg to about 600 mg/day of a compound of the present invention. Preferred daily doses generally will be from about 15 mg to about 80 mg/day.

[0156] The compounds of this invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds preferably are formulated prior to administration, the selection of which will be decided by the attending physician. Thus, another aspect of the present invention is a pharmaceutical composition comprising an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, optionally containing an effective amount of estrogen or progestin, and a pharmaceutically acceptable carrier, diluent, or excipient.

[0157] The total active ingredients in such formulations comprises from 0.1% to 99.9% by weight of the formulation. By "pharmaceutically acceptable" it is meant the carrier, diluent, excipients, and salt must be compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

[0158] Pharmaceutical formulations of the present invention can be prepared by procedures known in the art using well known and readily available ingredients. For example, the compounds of formula I, with or without an estrogen or progestin compound, can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinylpyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

[0159] The compounds also can be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for example, by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular physiological location, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

[0160] Compounds of formula I, alone or in combination with a pharmaceutical agent of the present invention, generally will be administered in a convenient formulation. The following formulation examples illustrate the present invention.

Formulations

[0161] In the formulations which follow, "active ingredient" means a compound of formula I, or a salt thereof.

Formulation 1: Gelatin Capsules

[0162] Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.1 - 1000
Starch, NF	0 - 650
Starch flowable powder	0 - 650

(continued)

Ingredient	Quantity (mg/capsule)
Silicone fluid 350 centistokes	0 - 15

[0163] The formulation above may be changed in compliance with the reasonable variations provided.

[0164] A tablet formulation is prepared using the ingredients below:

Formulation 2: Tablets

[0165]

Ingredient	Quantity (mg/tablet)
Active ingredient	2.5 - 1000
Cellulose, microcrystalline	200 - 650
Silicone dioxide, fumed	10 - 650
Stearate acid	5 - 15

The components are blended and compressed to form tablets.

[0166] Alternatively, tablets each containing 2.5 - 1000 mg of active ingredient are made up as follows:

Formulation 3: Tablets

[0167]

Ingredient	Quantity (mg/tablet)
Active ingredient	25 - 1000
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

[0168] The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

[0169] Suspensions each containing 0.1 - 1000 mg of medicament per 5 ml dose are made as follows:

Formulation 4: Suspensions

[0170]

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.1 - 1000 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

An aerosol solution is prepared containing the following ingredients:

Formulation 5: Aerosol

[0171]

Ingredient	Quantity (% by weight)
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00

[0172] The active ingredient is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to 30° C, and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remaining propellant. The valve units are then fitted to the container.

Suppositories are prepared as follows:

Formulation 6: Suppositories

[0173]

Ingredient	Quantity (mg/suppository)
Active ingredient	250
Saturated fatty acid glycerides	2,000

[0174] The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimal necessary heat. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

An intravenous formulation is prepared as follows:

Formulation 7: Intravenous Solution

[0175]

Ingredient	Quantity
Active ingredient	50 mg
Isotonic saline	1,000 mL

[0176] The solution of the above ingredients is intravenously administered to a patient at a rate of about 1 mL per minute.

Formulation 8: Combination Capsule I

[0177]

Ingredient	Quantity (mg/capsule)
Active ingredient	50
Premarin	1
Avicel pH 101	50
Starch 1500	117.50
Silicon Oil	2
Twen 80	0.50

(continued)

Ingredient	Quantity (mg/capsule)
Cab-O-Sil	0.25

Formulation 9: Combination Capsule II

[0178]

Ingredient	Quantity (mg/capsule)
Active ingredient	50
Norethynodrel	5
Avicel pH 101	82.50
Starch 1500	90
Silicon Oil	2
Tween 80	0.50

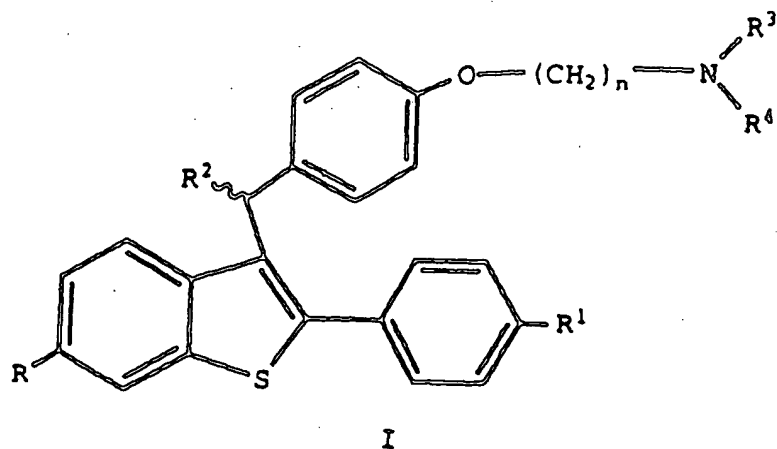
Formulation 10: Combination Tablet

[0179]

Ingredient	Quantity (mg/capsule)
Active ingredient	50
Premarin	1
Corn Starch NF	50
Povidone, K29-32	6
Avicel pH 101	41.50
Avicel pH 102	136.50
Crospovidone XL10	2.50
Magnesium Stearate	0.50
Cab-O-Sil	0.50

Claims

1. A compound of formula I



wherein

R is -H, -OH, -O(C₁-C₄ alkyl), -O-CO-(C₁-C₆ alkyl), -O-CO-Ar in which Ar is optionally substituted phenyl, or -O-SO₂-(C₄-C₆ alkyl);

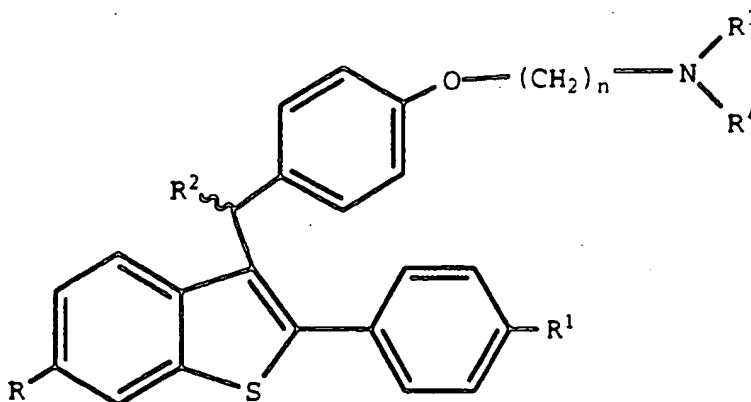
R¹ is -H, -OH, -O(C₁-C₄ alkyl), -O-CO-(C₁-C₆ alkyl), -O-CO-Ar in which Ar is optionally substituted phenyl, or -O-SO₂-(C₄-C₆ alkyl), chloro or bromo;

R² is -H or -OH

n is 2 or 3;

R³ and R⁴ each independently C₁-C₄ alkyl, or combine to form 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, or 1-hexamethyleimino; or a pharmaceutically acceptable salt thereof; other than the compound 2-(4-hydroxyphenyl)-3-[4-(2-piperidin-1-ylethoxy)-benzyl]benzo[b]thiophene-6-ol.

2. A compound according to Claim 1 wherein n is 2, and R³ and R⁴ combine to form 1-piperidinyl, or a pharmaceutically acceptable salt thereof,
3. A compound according to Claim 2 wherein R and R¹ each are -OH, or a pharmaceutically acceptable salt thereof.
4. A compound according to Claim 2 wherein R and R¹ each are -OCH₃, or a pharmaceutically acceptable salt thereof.
5. A compound as claimed in any one of Claims 1 to 4 wherein R² is -H.
6. A compound according to Claim 5 wherein said salt thereof is the hydrochloride salt.
7. A pharmaceutical composition comprising as an active ingredient a compound as claimed in any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, and, optionally, estrogen or progestin, associated with one or more pharmaceutically acceptable carriers, diluents, or excipients.
8. A pharmaceutical composition according to Claim 7 wherein R² of said formula I compound is -H, and said salt thereof is the hydrochloride salt.
9. A compound as claimed in any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, and, optionally estrogen or progestin, for use as an agent for alleviating the symptoms of post-menopausal syndrome, particularly osteoporosis, cardiovascular disease including hyperlipidemia, and estrogen-dependent cancer including breast and uterine cancer, and inhibiting uterine fibroid disease, endometriosis, aortal smooth muscle cell proliferation, and restenosis.
10. A compound according to Claim 9 wherein R² of said formula I compound is -H, and said salt thereof is the hydrochloride salt.
11. A process for preparing a compound of formula I



I

wherein

R is -H, -OH, -O(C₁-C₄ alkyl), -O-CO-(C₁-C₆ alkyl), -O-CO-Ar in which Ar is optionally substituted phenyl, or -O-SO₂-(C₄-C₆ alkyl);

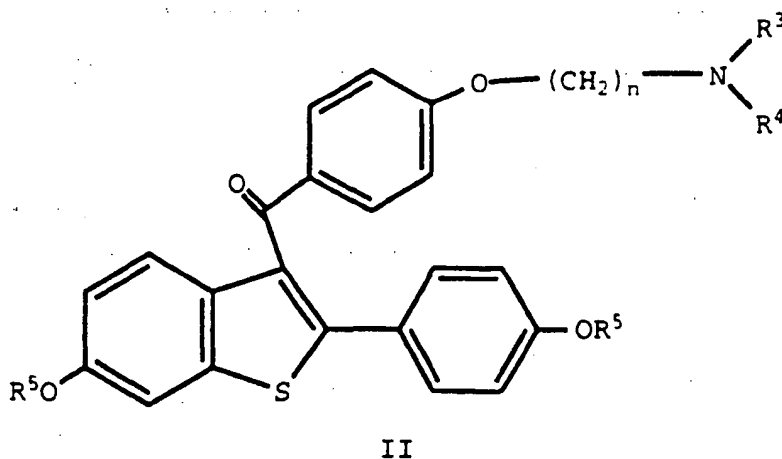
R¹ is -H, -OH, -O(C₁-C₄ alkyl), -O-CO-(C₁-C₆ alkyl), -O-CO-Ar in which Ar is optionally substituted phenyl, -O-SO₂-(C₄-C₆ alkyl), chloro or bromo;

R² is -H or -OH;

n is 2 or 3;

R³ and R⁴ each are independently C₁-C₄ alkyl, or combine to form 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, or 1-hexamethyleneimino; or a pharmaceutically acceptable salt thereof, which comprises

a) optionally removing the R⁵ hydroxy protecting groups of a compound of formula II



wherein

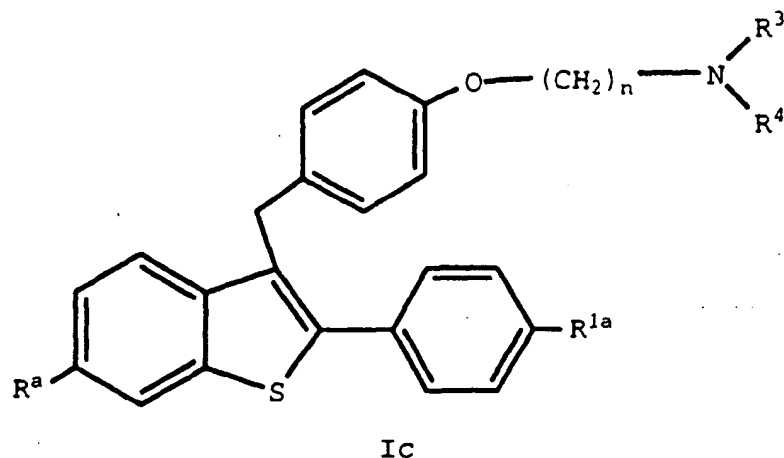
n, R³, R⁴, and R⁵ are as defined above, or a salt thereof;

b) reacting said formula II compound with a reducing agent;

c) when R and/or R¹ are -OH, optionally replacing said hydroxy groups with a substituent of the formula -O(C₁-C₄ alkyl), -OCOC₆H₅, -OCO(C₁-C₆ alkyl), or -OSO₂(C₄-C₆ alkyl); and

d) optionally salifying the reaction product from step b) or c).

12. A process according to Claim 11 for preparing a compound of formula Ic



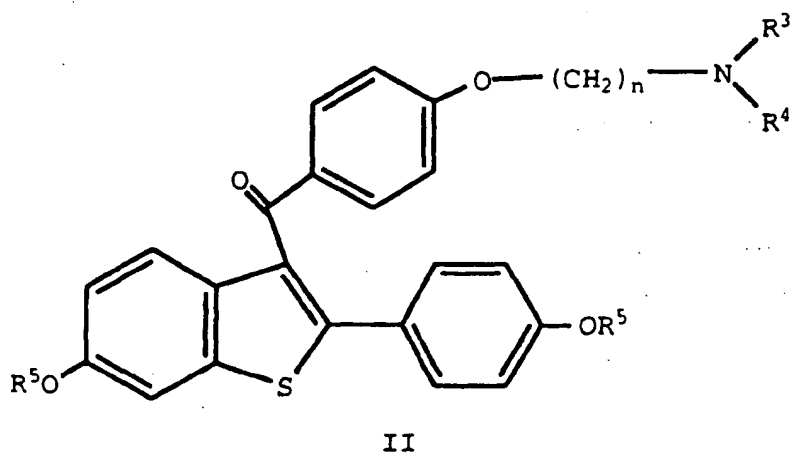
wherein

R^a and R^{1a} each are -OH or -OR⁵;

R^3 and R^4 each are independently C₁-C₄ alkyl, or combine to form 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidino, dimethyl-1-piperidinyl, 4-morpholino, or 1-hexamethyleneimino; and

R^5 is a hydroxy protecting group capable of resisting reduction by a strong reducing agent; or a pharmaceutically acceptable salt thereof, which comprises

a) optionally removing the R^5 hydroxy protecting groups of a compound of formula II



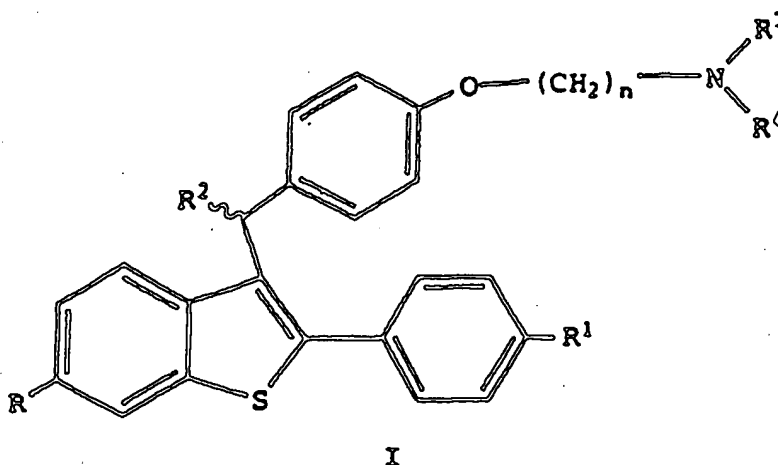
wherein n, R^3 , R^4 , and R^5 are as defined above, or a salt thereof;

b) reacting said formula II compound with a reducing agent in the presence of a solvent having a boiling point in the range from about 150° C to about 200° C, and heating the mixture to reflux; and

c) optionally salifying the reaction product from step b).

Patentansprüche

1. Verbindung der Formel I



worin

R für -H, -OH, -O(C₁-C₄ Alkyl), -OCO(C₁-C₆ Alkyl), -O-CO-Ar, worin Ar für wahlweise substituiertes Phenyl steht, oder -OSO₂(C₄-C₆ Alkyl) steht,

R¹ für -H, -OH, -O(C₁-C₄ Alkyl), -OCO(C₁-C₆ Alkyl), -O-CO-Ar, worin Ar für wahlweise substituiertes Phenyl steht, oder -OSO₂(C₄-C₆ Alkyl), Chlor oder Brom steht,

R² für -H oder -OH steht,

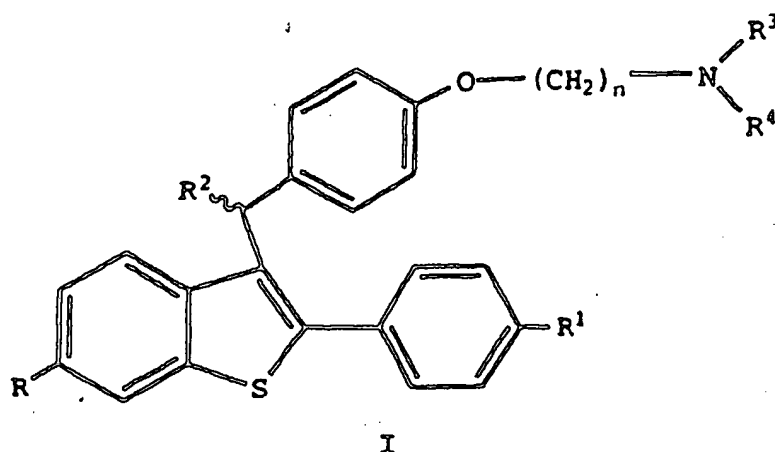
n für 2 oder 3 steht,

R³ und R⁴ jeweils unabhängig für C₁-C₄ Alkyl stehen, oder unter Bildung von 1-Piperidinyl, 1-Pyrrolidinyl, Methyl-1-pyrrolidinyl, Dimethyl-1-pyrrolidinyl, 4-Morpholino oder 1-Hexamethylenimino kombinieren, oder ein pharmazeutisch annehmbares Salz hiervon,

wobei sie nicht die Verbindung 2-(4-Hydroxyphenyl)-3-[4-(2-piperidin-1-ylethoxy)benzyl]benzo[b]thiophen-6-ol ist.

2. Verbindung nach Anspruch 1, worin n für 2 steht und R³ und R⁴ unter Bildung von 1-Piperidinyl kombinieren, oder ein pharmazeutisch annehmbares Salz hiervon.
3. Verbindung nach Anspruch 2, worin R und R¹ jeweils für -OH stehen, oder ein pharmazeutisch annehmbares Salz hiervon.
4. Verbindung nach Anspruch 2, worin R und R¹ jeweils für -OCH₃ stehen, oder ein pharmazeutisch annehmbares Salz hiervon.
5. Verbindung nach einem der Ansprüche 1 bis 4, worin R² für -H steht.
6. Verbindung nach Anspruch 5, worin das Salz hiervon das Hydrochloridsalz ist.
7. Pharmazeutische Zusammensetzung, die als Wirkstoff eine Verbindung nach einem der Ansprüche 1 bis 4 oder ein pharmazeutisch annehmbares Salz hiervon und wahlweise Östrogen oder Progestin zusammen mit einem oder mehreren pharmazeutisch annehmbaren Trägern, Verdünnungsmitteln oder Hilfsstoffen enthält.
8. Pharmazeutische Zusammensetzung nach Anspruch 7, worin R² der Verbindung der Formel I für -H steht, und das Salz hiervon das Hydrochloridsalz ist.
9. Verbindung nach einem der Ansprüche 1 bis 4 oder ein pharmazeutisch annehmbares Salz hiervon und wahlweise Östrogen oder Progestin zur Verwendung als Mittel zur Linderung der Symptome des postmenopausalen Syndroms, insbesondere der Osteoporose, kardiovaskulären Erkrankung einschließlich Hyperlipidämie, und Östrogenabhängigem Krebs einschließlich Brust- und Uteruskrebs, und zur Hemmung der fibroiden Uteruserkrankung, Endometriose, Proliferation der glatten Muskelzellen der Aorta und Restenose.
10. Verbindung nach Anspruch 9, worin R² der Verbindung der Formel I für -H steht, und das Salz hiervon das Hydrochloridsalz ist.

11. Verfahren zur Herstellung einer Verbindung der Formel I



worin

R für -H, -OH, -O(C₁-C₄ Alkyl), -OCO(C₁-C₆ Alkyl), -O-CO-Ar, worin Ar für wahlweise substituiertes Phenyl steht, oder -OSO₂(C₄-C₆ Alkyl) steht,

R¹ für -H, -OH, -O(C₁-C₄ Alkyl), -OCO(C₁-C₆ Alkyl), -O-CO-Ar, worin Ar für wahlweise substituiertes Phenyl steht, oder -OSO₂(C₄-C₆ Alkyl), Chlor oder Brom steht,

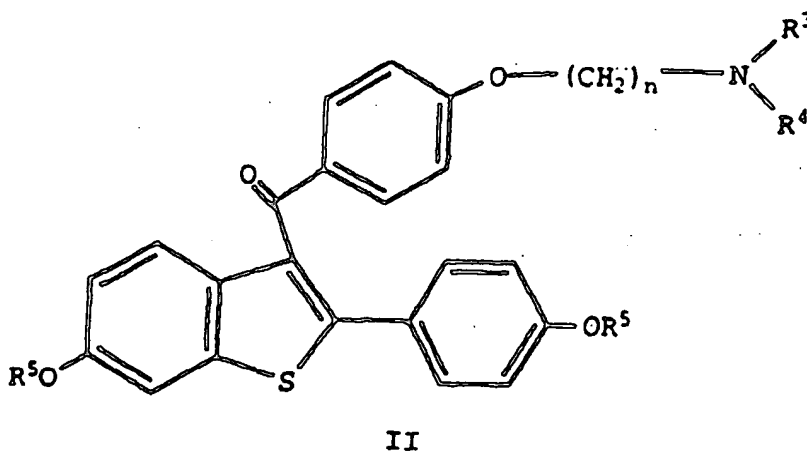
R² für -H oder -OH steht,

n für 2 oder 3 steht,

R³ und R⁴ jeweils unabhängig für C₁-C₄ Alkyl stehen, oder unter Bildung von 1-Piperidinyl, 1-Pyrrolidinyl, Methyl-1-pyrrolidinyl, Dimethyl-1-pyrrolidinyl, 4-Morpholino oder 1-Hexamethylenimino kombinieren, oder eines pharmazeutisch annehmbaren Salzes hiervon,

gekennzeichnet durch

a) wahlweise Entfernung der R⁵ Hydroxyschutzgruppen einer Verbindung der Formel II



worin

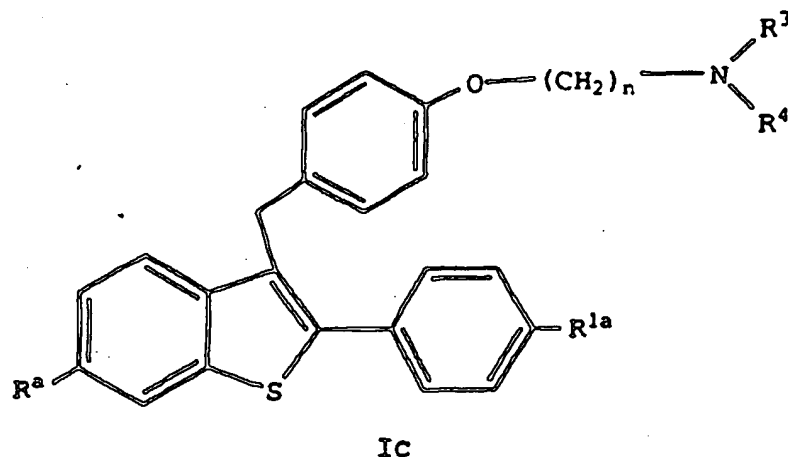
n, R³, R⁴ und R⁵ wie oben definiert sind, oder eines Salzes hiervon,

b) Umsetzung der Verbindung der Formel II mit einem Reduktionsmittel,

c) wenn R und/oder R¹ für -OH stehen, wahlweise Ersetzen der Hydroxygruppen mit einem Substituenten der Formel -O(C₁-C₄ Alkyl), -OCOC₆H₅, -OCO(C₁-C₆ Alkyl) oder -OSO₂(C₄-C₆ Alkyl) und

d) wahlweise Salzbildung mit dem Reaktionsprodukt von Schritt b) oder c).

12. Verfahren nach Anspruch 11 zur Herstellung einer Verbindung der Formel Ic



worin

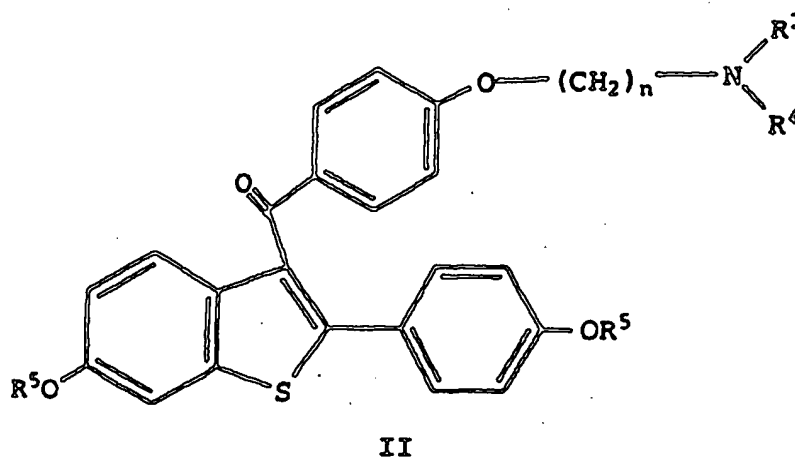
R^a und R^{1a} jeweils für -OH oder -OR⁵ stehen,

R³ und R⁴ jeweils unabhängig für C₁-C₄ Alkyl stehen oder unter Bildung von 1-Piperidinyl, 1-Pyrrolidinyl, Methyl-1-pyrrolidino, Dimethyl-1-piperidinyl, 4-Morpholino oder 1-Hexamethylenimino kombinieren, und

R⁵ für eine Hydroxyschutzgruppe steht, die einer Reduktion durch ein starkes Reduktionsmittel standhält, oder eines pharmazeutisch annehmbaren Salzes hiervon,

gekennzeichnet durch

a) wahlweise Entfernung der R⁵ Hydroxyschutzgruppen einer Verbindung der Formel II



worin

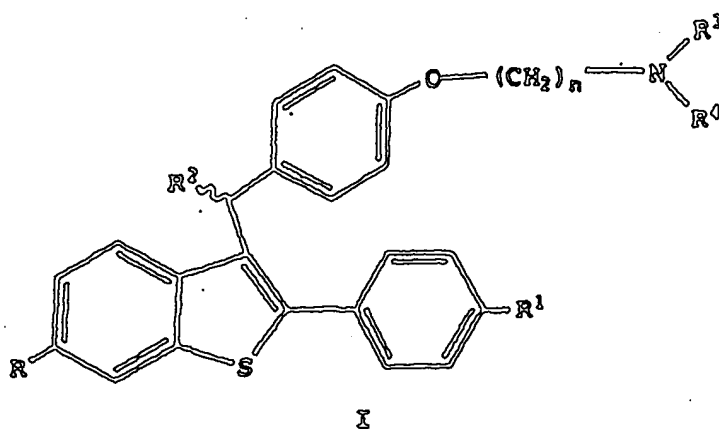
n, R³, R⁴ und R⁵ wie oben definiert sind, oder eines Salzes hiervon,

b) Umsetzung der Verbindung der Formel II mit einem Reduktionsmittel in Gegenwart eines Lösemittels mit einem Siedepunkt im Bereich von etwa 150°C bis etwa 200°C, und Erhitzen des Gemisches auf Rückfluß, und

c) wahlweise Salzbildung mit dem Reaktionsprodukt von Schritt b).

Revendications

1. Composé répondant à la formule I



dans laquelle

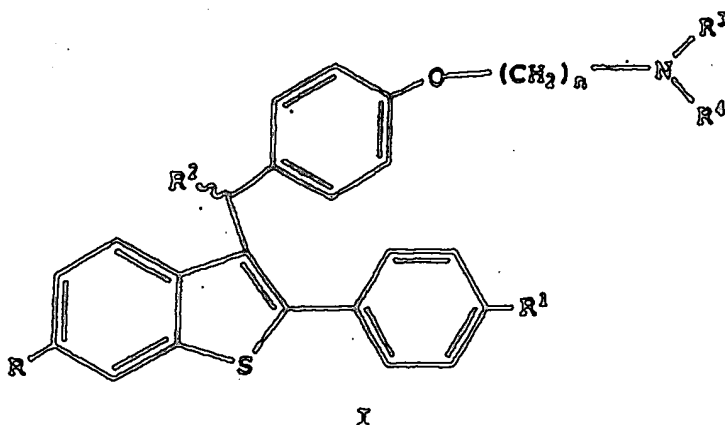
- R représente un atome d'hydrogène, un groupe -OH, un groupe -O-(alkyle en C₁-C₄), un groupe -O-CO-(alkyle en C₁-C₆), un groupe -O-CO-Ar dans lequel Ar représente un groupe phényle le cas échéant substitué, ou encore un groupe -O-SO₂-(alkyle en C₄-C₆);
- R¹ représente un atome d'hydrogène, un groupe -OH, un groupe -O-(alkyle en C₁-C₄), un groupe -O-CO-(alkyle en C₁-C₆), un groupe -O-CO-Ar dans lequel Ar représente un groupe phényle le cas échéant substitué, ou encore un groupe -O-SO₂-(alkyle en C₄-C₆), un atome de chlore ou un atome de brome ;
- R² représente un atome d'hydrogène ou un groupe -OH ;
- n est égal à 2 ou 3 ;
- R³ et R⁴ représentent, chacun indépendamment l'un de l'autre, un groupe alkyle en C₁-C₄, ou bien se combinent pour former un groupe 1-pipéridinyle, un groupe 1-pyrrolidinyle, un groupe méthyl-1-pyrrolidinyle, un groupe diméthyl-1-pyrrolidinyle, un groupe 4-morpholino ou un groupe 1-hexaméthylène-imino ;

ou un de ses sels pharmaceutiquement acceptables, autre que le composé 2-(4-hydroxyphényle)-3-[4-(2-pipéridin-1-yléthoxy)benzyl]benzo[b]thiophén-6-ol.

2. Composé selon la revendication 1, dans lequel n est égal à 2 et R³ et R⁴ se combinent pour former un groupe 1-pipéridinyle, ou un de ses sels pharmaceutiquement acceptables.
3. Composé selon la revendication 2, dans lequel R et R¹ représentent chacun un groupe -OH, ou un de ses sels pharmaceutiquement acceptables.
4. Composé selon la revendication 2, dans lequel R et R¹ représentent chacun un groupe -OCH₃, ou un de ses sels pharmaceutiquement acceptables.
5. Composé selon l'une quelconque des revendications 1 à 4, dans lequel R² représente un atome hydrogène.
6. Composé selon la revendication 5, dans lequel ledit sel dont il est question est le sel chlorhydrate.
7. Composition pharmaceutique comprenant, à titre d'ingrédient actif, un composé selon l'une quelconque des revendications 1 à 4, ou un de ses sels pharmaceutiquement acceptables, et le cas échéant des oestrogènes ou des progestatifs, en association avec un ou plusieurs supports, diluants ou excipients pharmaceutiquement acceptables.
8. Composition pharmaceutique selon la revendication 7, dans laquelle R² dudit composé répondant à la formule I

représente un atome d'hydrogène et ledit sel dont il est question est le sel chlorhydrate.

9. Composé selon l'une quelconque des revendications 1 à 4, ou un de ses sels pharmaceutiquement acceptables, et le cas échéant des oestrogènes ou des progestatifs, à utiliser comme agent pour soulager les symptômes du syndrome postménopausique, en particulier l'ostéoporose, les maladies cardio-vasculaires y compris l'hyperlipidémie, et les cancers dépendant des oestrogènes y compris le cancer du sein et de l'utérus, et pour inhiber le fibrome utérin, l'endométriose, la prolifération des cellules des muscles lisses de l'aorte et la resténose.
10. Composé selon la revendication 9, dans laquelle R^2 dudit composé répondant à la formule I représente un atome d'hydrogène et ledit sel dont il est question est le sel chlorhydrate.
11. Procédé pour préparer un composé répondant à la formule

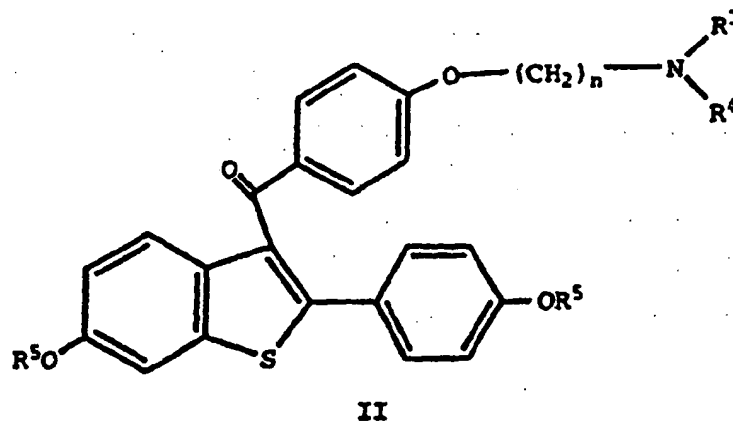


dans laquelle

- R représente un atome d'hydrogène, un groupe -OH, un groupe -O-(alkyle en C_1-C_4), un groupe -O-CO-(alkyle en C_1-C_6), un groupe -O-CO-Ar dans lequel Ar représente un groupe phényle le cas échéant substitué, ou encore un groupe -O-SO₂-(alkyle en C_4-C_6);
- R^1 représente un atome d'hydrogène, un groupe -OH, un groupe -O-(alkyle en C_1-C_4), un groupe -O-CO-(alkyle en C_1-C_6), un groupe -O-CO-Ar dans lequel Ar représente un groupe phényle le cas échéant substitué, ou encore un groupe -O-SO₂-(alkyle en C_4-C_6), un atome de chlore ou un atome de brome ;
- R^2 représente un atome d'hydrogène ou un groupe -OH ;
- n est égal à 2 ou 3 ;
- R^3 et R^4 représentent, chacun indépendamment l'un de l'autre, un groupe alkyle en C_1-C_4 , ou bien se combinent pour former un groupe 1-pipéridinyle, un groupe 1-pyrrolidinyle, un groupe méthyl-1-pyrrolidinyle, un groupe diméthyl-1-pyrrolidinyle, un groupe 4-morpholino ou un groupe 1-hexaméthylène-imino ;

ou un de ses sels pharmaceutiquement acceptables, qui comprend le fait de

- a) éliminer le cas échéant les groupes R^5 protecteurs du groupe hydroxyle d'un composé répondant à la formule II



dans laquelle

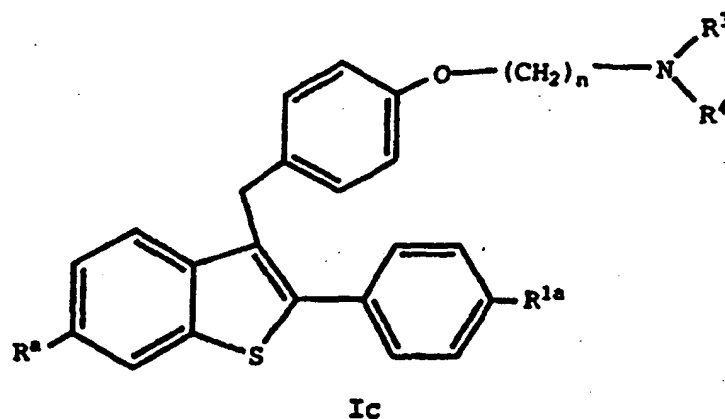
n , R^3 , R^4 et R^5 sont tels que définis ci-dessus, ou un de ses sels ;

b) faire réagir ledit composé répondant à la formule II avec un agent de réduction ;

c) lorsque R et/ou R^1 représentent un groupe $-OH$, remplacer le cas échéant lesdits groupes hydroxyle par un substituant choisi parmi le groupe comprenant un groupe $-O$ -(alkyle en C_1-C_4), un groupe $-OCOC_6H_5$, un groupe $-OCO$ -(alkyle en C_1-C_6) ou encore un groupe $-O-SO_2$ -(alkyle en C_4-C_6) ; et

d) le cas échéant salifier le produit réactionnel de l'étape b) ou de l'étape c).

12. Procédé selon la revendication 11, pour préparer un composé répondant à la formule Ic



dans laquelle

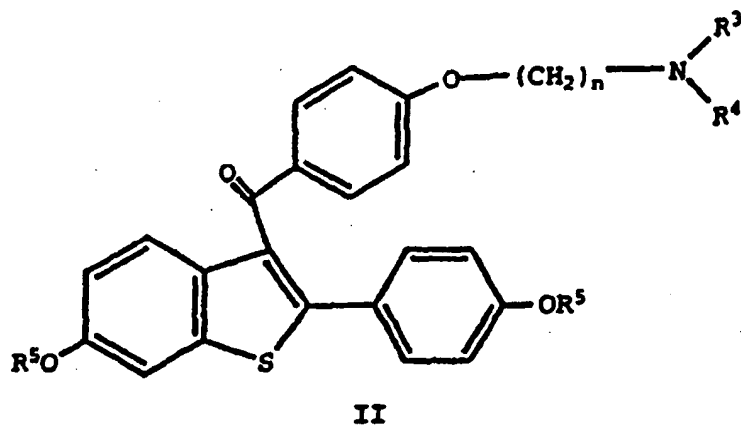
R^a et R^{1a} représentent chacun un groupe $-OH$ ou un groupe $-OR^5$;

R^3 et R^4 représentent chacun, indépendamment l'un de l'autre, un groupe alkyle en C_1-C_4 , ou bien se combinent pour former un groupe 1-pipéridinyle, un groupe 1-pyrrolidinyle, un groupe méthyl-1-pyrrolidino, un groupe diméthyl-1-pipéridinyle, un groupe 4-morpholino ou un groupe 1-hexaméthylène-imino ; et

R^5 représente un groupe protecteur du groupe hydroxyle capable de résister à une réduction via un agent de réduction fort ;

ou un de ses sels pharmaceutiquement acceptables, qui comprend le fait de

a) éliminer le cas échéant les groupes R^5 protecteurs du groupe hydroxyle d'un composé répondant à la formule II



dans laquelle

n, R³, R⁴ et R⁵ sont tels que définis ci-dessus, ou un de ses sels ;

b) faire réagir ledit composé répondant à la formule II avec un agent de réduction en présence d'un solvant dont le point d'ébullition se situe dans la plage d'environ 150 °C à environ 200 °C, et chauffer le mélange à reflux ; et

c) le cas échéant salifier le produit réactionnel de l'étape b).